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(54) Title: COMBINATORIAL LIBRARIES OF MONOSACCHARIDES

(57) Abstract: The present invention provides a monosaccharide compound of general formula I as shown in the specification. The invention also provides processes for the preparation of the compound of formula I and methods of screening for antibacterial or antibiotic compounds involving the compound of formula I.

COMBINATORIAL LIBRARIES OF MONOSACCHARIDES

FIELD OF THE INVENTION

This invention relates to monosaccharide compounds, methods for their preparation and their use in producing combinatorial libraries of potentially biologically active mono-or oligosaccharide compounds.

The compounds of the invention are variously functionalized, with a view to varying lipid solubility, size, function and other properties, with the particular aim of the discovery of novel drug or drug-like compounds, or compounds with useful properties. The invention provides intermediates, processes and synthetic strategies for the solution or solid phase synthesis of various amides of α- and β-*D*-glucosamine and -galactosamine, their PEG-glycosides and other glycosides, with various functionality about the sugar ring, including the addition of aromaticity, and the placement of amino acid and peptide units or their isosteres.

These compounds are structural mimetics of the substrates of enzymes in the muramyl pathway in peptidoglycan biosynthesis. It is expected that compounds of the type proposed, or analogues thereof, will act as inhibitors of the formation of the peptidoglycan layers that protect bacterial cell membranes or as inhibitors of other bacterial enzymes. Thus compounds of this type are attractive targets for the discovery of new antibiotics and antibacterials.

BACKGROUND OF THE INVENTION

Since the discovery of penicillin in 1928 the apparent ability of the ever-growing numbers of available antibiotics to treat infections and disease has, until recently, caused a high degree of complacency about the threat of bacterial resistance. This complacency has created a situation where antibiotics are over-prescribed in both hospitals and in the community, and used

extensively in animal feeds. The alarming speed with which bacteria have become resistant to microbial agents has meant that there is a very real danger that infections, which were until recently completely controllable, will pose serious threats to human health.

All unicellular bacteria contain a cell wall which is associated with a diverse range of functions, although the major one is that of protecting the cell from lysing under high internal osmotic pressures. The cell wall is composed of peptidoglycan, a rigid mesh of β-1,4-linked carbohydrate polymers covalently cross-linked by peptide chains. The peptidoglycan synthetic pathway is not present in mammalian systems, suggesting that the side-effects associated with such inhibitors could be minimized. Thus the bacterial peptidoglycan biosynthetic pathway presents an opportunity for the development of novel antibacterial agents.

There is a great deal of interest in the substrates of the muramyl pathway and their analogues, and in the synthesis of related compounds that may result in new therapeutics. Tanner and co-workers have recently prepared compounds that inhibit the MurD and MurE enzymes of the muramyl pathway. These non-carbohydrate compounds have the sugar and lactate moieties of a muramic acid-like compound replaced with a five carbon linker unit (Zeng, B., Wong, K.K., Pompliano, D.L., , Reddy, S., and Tanner, M.E., JOC **1998** 63(26) 10081-5; Tanner, M.E., Vaganay, S., van Heijenoort, J., and Blanot, D., JOC **1996** 61(5) 1756-60), and are prepared by standard organic chemistry techniques. They are linear, flexible organic compounds with substituents that resemble those of UDP-MurNAc-pentapeptide (the "Park Nucleotide" (Park, J. *J. Biol. Chem.* **1952**, *194*, 877)). One of those compounds in particular was found to be a relatively potent inhibitor of MurE (Zeng, B., Wong, K.K., Pompliano, D.L. , Reddy, S., and Tanner, M.E.JOC **1998** 63(26) 10081-5).

In other studies on an analogous phosphinate inhibitor of MurD, it was found that retaining the MurNAc

sugar residue, instead of replacing it with a carbon linker unit, increases the potency of the inhibitor by almost two orders of magnitude (Gegnas, L. D., Waddell, S. T., Chabin, R. M., Reddy, S., Wong, K. K., *Bioorg. Med. Chem. Lett.* **1998** *8* 1643). This suggests that building a library of monosaccharide analogues of the substrates of the muramyl pathway is an attractive proposition for the generation of new therapeutics which target that system.

One approach to the synthesis of such compounds is to make use of biosynthetic techniques, such as that used in preparing labelled versions or analogues of MurNAc from GlcNAc by implementing the MurA and MurB enzymes themselves (Lees, W.J., Benson, T.E., Hogle, J.M., and. Walsh. C.T., Biochemistry **1996**, 35(5), 1342-1351).

Chemical methods require protected building blocks, and some well-established chemistry has been implemented, using GlcNAc to yield the benzyl glycoside of N-acetyl-4,6-benzylidenemuramic acid (Jeanloz, R. W., Walker, E., Sinaÿ, P., Carbohydr. Res. **1968**, 6, 184). One challenge to the synthesis of such compounds is the alkylation of the C-3 position of the carbohydrate residue. In the natural muramyl system, the MurA and MurB enzymes add what is ultimately a lactate moiety to the C-3 position.

The addition of a lactate moiety at C-3 has been achieved chemically in a process in which the required materials were generated through the intermediate preparation of a nitroalkene sugar (Vega-Perez, et al. *Tetrahedron* **1999**, *55*, 9641-9650). An alternative approach is the alkylation of the C-3 hydroxyl with the α-bromide of an appropriately protected propianoic acid to generate the required compound (Iglesias-Guerra, F., Candela, J.I., Bautista, J., Alcudia, F., and Vega-Perez, J.M., *Carb.Res.* **1999**, *316*, 71-84).

Having compounds with a lactate moiety, or similar acid, in place at C-3 allowed the addition of amino acids to build the required pentapeptide substituent. This molecule was subsequently converted to the natural

substrates for the muramyl enzyme system (Hitchcock, C. N., Eid, J. A., Aikins, M.Z-E., and Blaszczak, L.C., J. Am. Chem. Soc. **1998**, 120(8), 1916). In a similar approach the preformed pentapeptide was added as a single unit to yield muramyl products (Ha, S., Chang, E., Lo,M-C., Men, H., Park, P., Ge, M., and Walker, S., J. Am. Chem. Soc. **1999**, 121(37), 8415).

Combinatorial chemistry and parallel synthesis have become the methods of choice for the rapid synthesis of a large number of related compounds simultaneously, and this approach has been used to produce libraries of compounds to be screened for biological activity. Sometimes such libraries are focussed to test for activity of the compounds so generated towards a particular biological agent or organism, although often large libraries are also prepared in a random fashion. Either way, the intended end result of combinatorial chemistry is the rapid discovery and optimization of leads for the development of new pharmaceuticals.

Despite the obvious advantages of a combinatorial approach to the preparation of compounds for drug discovery, this technique is underexplored in the field of carbohydrate chemistry. This is primarily because of the well-known difficulties associated with the synthesis of carbohydrate compounds. For that reason carbohydrate libraries prepared in the past have tended to be relatively simple. For example, Hindsgaul et al have produced a library of monosaccharide compounds by a combinatorial approach (Ole Hindsgaul US Patent 5780603); however, the variation in the compounds was limited to the glycosidic bond. A glycopeptide library in which mannose residues were decorated with various amino acids has been described, but these were conjugated to the sugar solely through the C-6 position (Tennant-Eyles, R.J., and Fairbanks, A.J., *Tetrahedron Asymmetry*. **1999**, 10, 391-401).

Access to greater variation has been attempted by making used of libraries of carbohydrate mimetics

(Byrgesen, E., Nielsen, J., Willert, M., and Bols, M., *Tetrahedron Lett.* **1997**, *38*, 5697-5700 and Lohse, A., Jensen, K.B., and Bols, M.,*Tetrahedron Lett.*, **1999**, *40*, 3033-3036). However, one approach which successfully added greater diversity to monosaccharides was that of Goebel and Ugi (*Tetrahedron Lett.*, **1995**, *36(34)*, 6043-6046) who generated a small library of alkylated glycals by subjecting protected glucals to electrophilic attack and then subsequent reactions. Unfortunately this method is limited by the fact that each starting glucal may give rise to a number of isomeric products.

For these reasons there is particular interest in libraries of aminoglycosides and amino sugars for drug discovery. Some work on such compounds has been published, with Silva and co-workers preparing impressive disaccharide libraries containing glucosamine (Silva,D.J., Wang, H., Allanson, N.M., Jain, R.K., and Sofia, M.J., JOC **1999**, 64(16), 5926-5929). However, this library still suffers from the limitation that the variation is limited solely to acylations of the amino group.

More variation, and in fact a three-dimensional diversity, was obtained in the preparation of amino sugars by Sofia and co-workers (Sofia, M.J., Hunter, R., Chan, T.Y., Vaughan, A., Dulina,R., Wang, H., and Gange, D., JOC **1998**, 63(9), 2802-2803). This allowed chemical diversity at three combinatorial sites on the sugar residue. Other workers have prepared a library of compounds with four (Wunberg, T., Kallus, C., Opatz, T., Henke, S., Schmidt, W., and Kunz, H., Angew. Chem. Int. Ed. 1998, 37(18), 2503-2505), and five (Kallus, C., Opatz, T., Wunberg, T., Schmidt, W., Henke, S., and Kunz, H., *Tetrahedron Lett.* **1999**, *40*, 7783-7786) such sites of functionalization, although these compounds were not amino-sugars.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of

these documents forms part of the common general knowledge in the art, in Australia or in any other country.

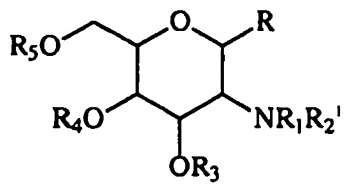
Hitherto, there have been few attempts to synthesise analogues of the muramyl substrates, particularly those which contain modifications at the anomeric position or at the C-2 nitrogen. The natural substrate and all of the muramyl enzyme intermediates contain exclusively the α-glycosidic diphosphate. Our modelling and design studies with the crystal structure of the Mur D enzyme suggest that both the α or β anomeric configuration of many of the compounds proposed in this invention can fit into the active site of this enzyme. We believe that this is the first time that β-glycosides which contain no phosphate groups have been prepared as potential inhibitors of the muramyl enzyme system.

Many of the traditional methods of carbohydrate synthesis have proved to be unsuitable to a combinatorial approach, particularly because modern high-throughput synthetic systems require that procedures to be readily automatable. The compounds and processes described herein are particularly suited to the solid and solution phase combinatorial synthesis of carbohydrate-based libraries, and are amenable to automation. The methods of the invention yield common intermediates which are suitably functionalized to provide diversity in the structure of the compounds so generated. In this way the technology described can produce many and varied compounds around the basic structure shown in formula I. Using this method, it is possible to introduce varied functionality in order to modulate both the biological activity and pharmacological properties of the compounds generated.

Thus the compounds and methods disclosed herein provide the ability to produce random or focussed combinatorial-type libraries not only for the discovery of new antibacterial agents, but also for the discovery of other novel drug or drug-like compounds, or compounds with other useful properties.

SUMMARY OF THE INVENTION

According to the present invention there is provided a monosaccharide compound of general formula I



I

in which the monosaccharide ring is of the glucosamine or galactosamine configuration;

R_4 and R_5 are hydrogen or together form an optionally substituted benzylidene acetal in which the optional substituent is chosen from halo, azido, alkoxy, nitro or alkyl;

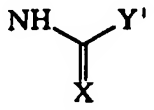
R_3 is hydrogen; optionally substituted glycolate or optionally substituted lactate or derivatives thereof; or a carboxylic acid mimetic;

R_1 is optionally substituted acyl, optionally substituted benzoyl, optionally substituted biphenylcarbonyl, heteroaryl acyl, optionally substituted bicycloacyl, optionally substituted bicycloheteroacyl, sulfonamide, urea or carbamates;

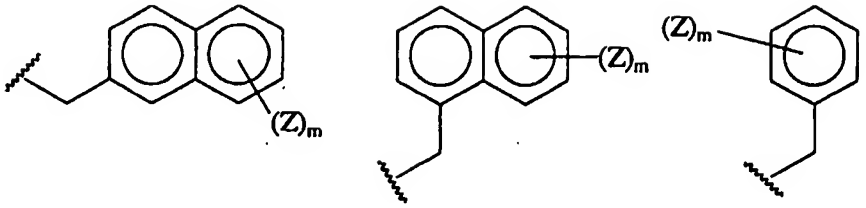
R_2' is hydrogen;

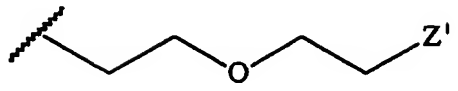
R_1 and R_2' together form succinimide, maleimide or optionally substituted phthalimide,

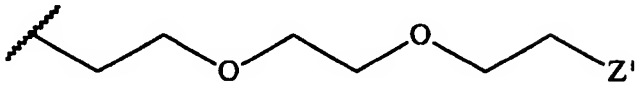
R is N_3, O-Y,

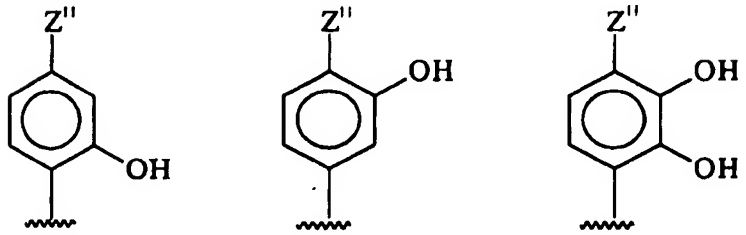
 or $-NH-SO_2-Y''$

in which Y is









in which Z is positioned on one or both of the aromatic rings of the bicyclic structures and is independently selected from OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, aryloxy, SO_2NH_2, amidine and guanidinium;

q is 0 or 1;

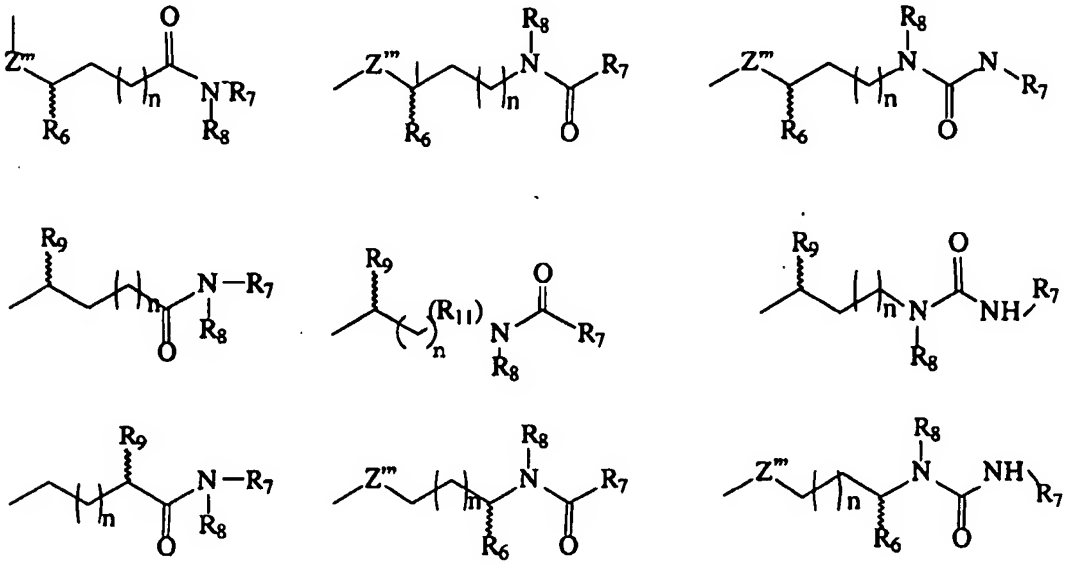
m is an integer of 0 to 3;

Z' is halo, optionally substituted S-aryl, optionally substituted S-heteroaryl, optionally substituted aryl or optionally substituted heteroaryl;

Z'' is an optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

X is O, NH or S;

Y' is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted arylalkyl, optionally substituted heteroaryl alkyl,



in which Z''' is O,NH or S;

R_6 is H, $CONH_2$ or COOH ;

n is an integer of 0 to 4 ;

R_7 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl or optionally substituted heteroarylalkyl

R_8 is H, OH, NH_2, alkyl, alkenyl or alkynyl;

R_9 is H, OH, NH_2, or $NHCO-R_{10}$ in which R_{10} is an optionally substituted alkyl;

R_{11} is an optionally substituted alkylene, optionally substituted cycloalkyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl; and

Y'' is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted arylalkyl or optionally substituted heteroaryl alkyl,

derivatives thereof, tautomers thereof and/or isomers thereof.

The term "derivatives" is used herein in its broadest sense to include protected forms and synthetic precursors of compounds of the present invention, for example, azide is a protected form/precursor of amine, nitrile is a protected form/precursor of amine, carboxylic acid and amide.

The term "tautomer" is used herein in its broadest sense to include compounds of formula I which are capable of existing in a state of equilibrium between two isomeric forms. Such compounds may differ in the bond connecting two atoms or groups and the position of these atoms or groups in the compound.

The term "isomer" is used herein in its broadest sense and includes structural, geometric and stereo isomers. As the compound of formula I may have one or more chiral centres, its is capable of existing in enantiomeric forms. The anomeric centre of the monosaccharide ring may also be of either the α or β configuration.

The term "halo" denotes fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine.

The term "alkyl" used either alone or in compound words such as "optionally substituted alkyl", "optionally substituted cycloalkyl", "arylalkyl" or "heteroarylalkyl", denotes straight chain, branched or cyclic alkyl, preferably C_{1-6}alkyl or cycloalkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylbexyl, 1-methylhexyl, 2,2-dimethypentyl, 3,3-

dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2 pentylheptyl and the like. Examples of cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term "alkylene" used either alone or in compound words such as "optionally substituted alkylene" denotes the same groups as "alkyl" defined above except that an additional hydrogen has been removed to form a divalent radical. It will be understood that the optional substituent may be attached to or form part of the alkylene chain.

The term "alkenyl" used either alone or in compound words such as "optionally substituted alkenyl" denotes groups formed from straight chain, branched or cyclic alkenes including ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as defined above, preferably C_{2-6}alkenyl. Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-

cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

The term "alkynyl" used either alone or in compound words, such as "optionally substituted alkynyl" denotes groups formed from straight chain, branched, or mono- or poly- or cyclic alkynes, preferably C_{2-6} alkynyl. Examples of alkynyl include ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexylnyl, 4-hexynyl, 5-hexynyl, 10-undecynyl, 4-ethyl-1-octyn-3-yl,7-dodecynyl, 9-dodecynyl, 10-dodecynyl, 3-methyl-1-dodecyn-3-yl, 2-tridecynyl, 11-tridecynyl, 3-tetradecynyl, 7-hexadecynyl, 3-octadecynyl and the like.

The term "alkoxy" used either alone or in compound words such as "optionally substituted alkoxy" denotes straight chain or branched alkoxy, preferably C_{1-7}alkoxy. Examples of alkoxy include methoxy, ethoxy, n-propyloxy, isopropyloxy and the different butoxy isomers.

The term "aryloxy" used either alone or in compound words such as "optionally substituted aryloxy" denotes aromatic, heteroaromatic, arylalkoxy or heteroaryl alkoxy, preferably C_{6-13} aryloxy. Examples of aryloxy include phenoxy, benzyloxy, 1-napthyloxy, and 2-napthyloxy.

The term "acyl" used either alone or in compound words such as "optionally substituted acyl" or "heteroarylacyl" denotes carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl or a heterocyclic ring which is referred to as heterocyclic acyl. Examples of acyl include carbamoyl; straight chain or branched alkanoyl such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, and icosanoyl; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, t-

butoxycarbonyl, t-pentyloxycarbonyl and heptyloxycarbonyl; cycloalkylcarbonyl such as cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; alkylsulfonyl such as methylsulfonyl and ethylsulfonyl; alkoxysulfonyl such as methoxysulfonyl and ethoxysulfonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthlpropanoyl and naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacrylyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); aralkoxycarbonyl such as phenylalkoxycarbonyl (e.g. benzyloxycarbonyl); aryloxycarbonyl such as phenoxycarbonyl and naphthyloxycarbonyl; aryloxyalkanoyl such as phenoxyacetyl and phenoxypropionyl; arylcarbamoyl such as phenylcarbamoyl; arylthiocarbamoyl such as phenylthiocarbamoyl; arylglyoxyloyl such as phenylglyoxyloyl and naphthylglyoxyloyl; arylsulfonyl such as phenylsulfonyl and naphthylsulfonyl; heterocycliccarbonyl; heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl; heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl and heterocyclichexenoyl; and heterocyclicglyoxyloyl such as thiazolylglyoxyloyl and thienyglyoxyloyl.

The term "aryl" used either alone or in compound words such as "optionally substituted aryl", "arylalkyl" or "heteroaryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbons or aromatic heterocyclic ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, phenoxyphenyl,

naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl, azulenyl, chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrryl, pyrrolyl, furanyl, imadazolyl, pyrrolydinyl, pyridinyl, piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. Preferably, the aromatic heterocyclic ring system contains 1 to 4 heteroatoms independently selected from N, O and S and containing up to 9 carbon atoms in the ring.

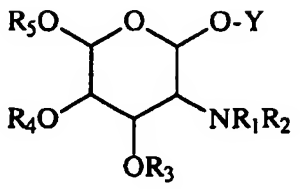
The term "heterocycle" used either alone or in compound words as "optionally substituted heterocycle" denotes monocyclic or polycyclic heterocyclyl groups containing at least one heteroatom atom selected from nitrogen, sulphur and oxygen. Suitable heterocyclyl groups include N-containing heterocyclic groups, such as, unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl; saturated to 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl, imidazolidinyl, piperidino or piperazinyl; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as, indolyl, isoindolyl, indolizinyl, benzimidazoyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl or tetrazolopyridazinyl; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, pyranyl or furyl; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms, such as, thienyl; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl or thiadiazolyl;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as thiazolidinyl; and
unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

In this specification "optionally substituted" means that a group may or may not be further substituted with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, carboxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, nitroso, azido, amidine, guanidium, amino, alkylamino, alkenylamino, alkynylamino, arylamino, benzylamino, acylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, acyloxy, aldehydo, alkylsulphonyl, arylsulphonyl, sulphonylamino, alkylsulphonylamino, arylsulphonylamino, alkylsulphonyloxy, arylsulphonyloxy, heterocyclyl, heterocycloxy, heterocyclylamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, sulfonic acid, alkylthio, arylthio, acylthio and peptidomimetics.

Preferred optional substituents include OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, aryloxy, SO_2NH_2, amidine, guandinium or peptidomimetics.

A preferred compound of formula I has the formula Ia



Ia

in which the monosaccharide ring is of the glucosamine or galactosamine configuration and the anomeric centre may be either the α or β configuration;

R_5, R_4 and R_3 are as defined in formula I above;

R_2 is hydrogen;

R_1 is

(i) C_{2-8} acyl which may be branched or linear and optionally substituted with one or more OH, SH, CF_3, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, aryloxy, SO_2NH_2, amidine or guanidinium;

(ii) a benzoyl group which may be optionally substituted with one or more OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium;

(iii) a biphenylcarbonyl group which may be optionally substituted on either one or both of the aromatic rings with one or more of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium; or

(iv) a heteroaryl acyl, sulfonamide, urea or carbamate;

R_1 and R_2 together form optionally substituted succinimide, optionally substituted maleimide or optionally substituted phthalimide;

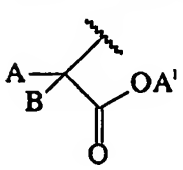
Y is as defined in formula I above in which the optional substituents for Z' or Z'' are at least one of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2,

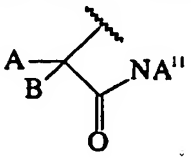
CO_2H, azido, nitroso, alkoxy, aryloxy, SO_2NH_2, amidine or guanidinium.

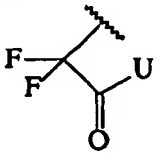
Preferably, the glycolate or lactate or derivatives thereof are optionally substituted with at least one amino acid or peptidomimetic.

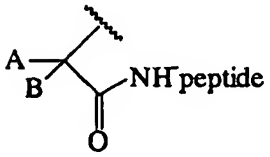
Examples of suitable peptidomimetic substiuents which may be used at R_3 are disclosed in Gante, J., *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 1699-1720 and Giannis, A., and Kolter, T., *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1244-1267).

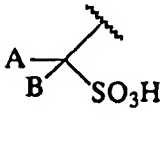
Non-limiting examples of carboxylic acid mimetics and other suitable substituents for R_3 are:

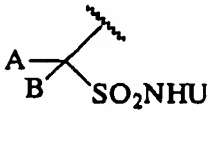


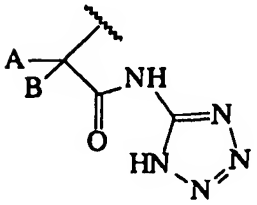


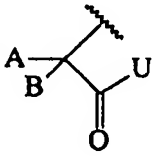


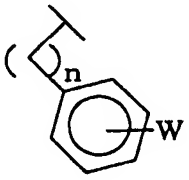












in which A and B are independently hydrogen, alkyl, trihaloalkyl or halo;

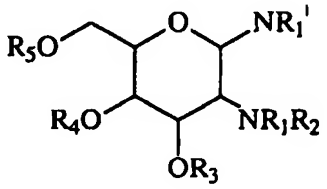
A' is hydrogen or alkyl;

A'' is hydroxy, optionally substituted amine or oxyaryl;

U is hydrogen, aryl, heteroaryl, alkyl, alkenyl or alkynyl each of which may be optionally substituted with one or more of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium; and

W is hydrogen or an acidic or acid mimetic, such as, for example, OH, SH, CF_3, NO_2, halo, SO_3H, CO_2H, azido, nitroso, alkoxy, aryloxy, SO_2NH_2, or forms a carbocyclic or heterocyclic ring.

Another preferred compound of formula I has the formula Ib



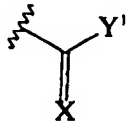
Ib

in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric centre may be of the α or β configuration;

R_5, R_4 and R_3 are as defined in formula I above;

R_2 and R_1 are as defined in formula Ia above;

R_1' is N_2 or

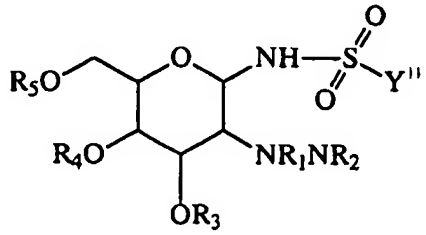


in which

X is O, NH or S; and

Y' is as defined in formula I above in which R_7 may be optionally substituted with at least one of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium.

A further preferred compound of formula I has the formula Ic



Ic

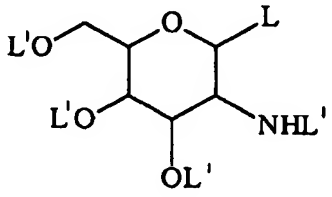
in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric center may be of the α or β configuration;

in which R_5, R_4 and R_3 are as defined in formula I above;

R_2 and R_1 are as defined in formula Ia above;

Y'' is as defined in formula I above and may be optionally substituted with one or more OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium.

The present invention also provides a method for the preparation of a compound of general formula I, comprising the step of glycosylating an intermediate compound of formula IV,



IV

in which L is a leaving group and L' is a protecting groups with an alcohol or phenol acceptor.

The leaving group may be of any suitable known type, such as, for example, those leaving groups disclosed in J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure" 4th Edition, pp 352-357, John Wily & Sons, New York, 1992 which is incorporated herein by reference. Preferably, the leaving group is acetate, thiomethyl, trichloroacetimidyl or halogen, more preferably bromine or chlorine.

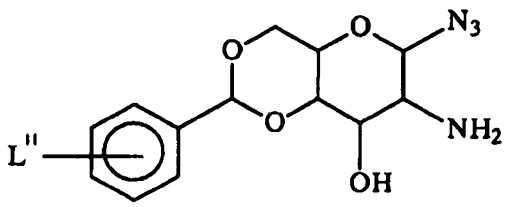
Suitable protecting groups include those disclosed in Greene, T.W., "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1981, such as optionally substituted silyl, optionally substituted alkyl, optionally substituted acyl or optionally substituted heteroacyl, for

example, azide or 4,4-dimethyl-2,6-dioxocyclohex-1-y-idene (Dde) , ^{t}butyldimethylsilyl, ^{t}butyldiphenylsilyl, benzylidene, 4-methoxybenzylidene, benzoate, acetate, chloroacetate, 9-fluorenylmethylcarbamate, benzyloxy carbamates, isopropylidene and 4-methoxyphenyl.

Examples of suitable alcohols include methanol, ethanol, propanol, iso-propanol, benzyl alcohol, 2',2-chloroethoxyethanol, 2'',2',2-chloroethoxyethoxyethanol, 2-napthylmethanol, 1-napthylmethanol, allyl alcohol, 5-penteneol, 4-buteneol, ^{t}butanol, sec-butanol and n-butanol.

Examples of suitable "phenol acceptor" include 4-nitrophenol, phenol, resorcinol, phloroglucinol, 4-chlorophenol, catechol and 4-allylphenol.

The present invention further provides a method for the preparation of a compound of formula I, in particular formula Ib or Ic, comprising the step of acylating an intermediate compound of general formula V



V

in which L'' is hydrogen, NO_2, halo, azido or alkoxy.

The compounds of the present invention are useful in screening for biological activity, particularly use of compounds of the formulae Ia, Ib and Ic for screening for anti-bacterial or antibiotic activity. In particular,

compounds of the invention are useful in screening for inhibitory activity against one or more enzymes of the muramyl cascade.

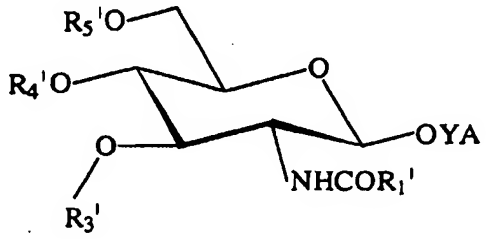
Thus, according to a further aspect of the present invention there is provided a method of screening for antibacterial or antibiotic compounds comprising the steps of:

(a) forming a combinatorial library comprising a compound of the formula I defined above; and

(b) testing the combinatorial library for antibacterial or antibiotic activity.

According to a still further aspect of the present invention there is provided an antibacterial or antibiotic compound identified using the method defined above.

In a particularly preferred embodiment for this purpose, the compound of formula Ia has structure A



Structure A

in which R_5' and R_4' are hydrogen or together form a benzylidene-type acetal;

R_3' is a lactate or lactate mimetic which may be optionally substituted with short peptides or peptidomimetics such as those found in the muramyl enzyme products;

R_1' is an acetyl group as in the naturally-occurring system; or

$NHCOR_1'$ may be other amides, sulfonamides, urea and the like; and

YA is a structural or functional mimetic of uridine diphosphate or a simple diphosphate.

Analogous compounds to Structure A of the formulae Ib and Ic of the invention are also contemplated as preferred embodiments for this purpose.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1 to 3 show HPLC and mass spectra for representative compounds produced following General Step 9.
Figure 1: 1-[2'-(2''-(4'''-chlorophenylthio)ethoxy)ethyl]-2-deoxy-2-benzoylamino-β-D-glucose. HPLC and mass spectrum.
Figure 2: 1-[2'-(2''-(2'''-(m-trifluoromethylphenylthio) ethoxy)ethoxy)ethyl]-2-deoxy-2-acetylamino-β-D-glucose. HPLC and mass spectrum.
Figure 3: 1-[2'-(2''-(2'''-(m,p-dichlorophenylthio) ethoxy)ethoxy)ethyl]-2-deoxy-2-(3',3',3'trimethylpropionylamino)-β-D-glucose. HPLC and mass spectrum.

Figure 4a shows a ^{1}Hnmr spectrum and Figure 4b shows a mass spectrum for a protected tripeptide product produced according to General step 10. 1-[2'-(2''-(2'''-chloroethoxy)ethoxy)ethyl]-2-deoxy-2-benzoylamino-4,6-O-benzylidene-3-O-methylcarbonyl-[((α-O-benzyl)-γ-glutamyl)-(N^{6}-(2'chlorobenzylcarbamoyl)-lysinyl)-(O-benzylalanyl)]-β-D-glucopyranoside.

DETAILED DESCRIPTION OF THE INVENTION

The invention will now be described in detail by way of reference only to the following non-limiting examples and to the drawings.

Abbreviations used herein are as follows:

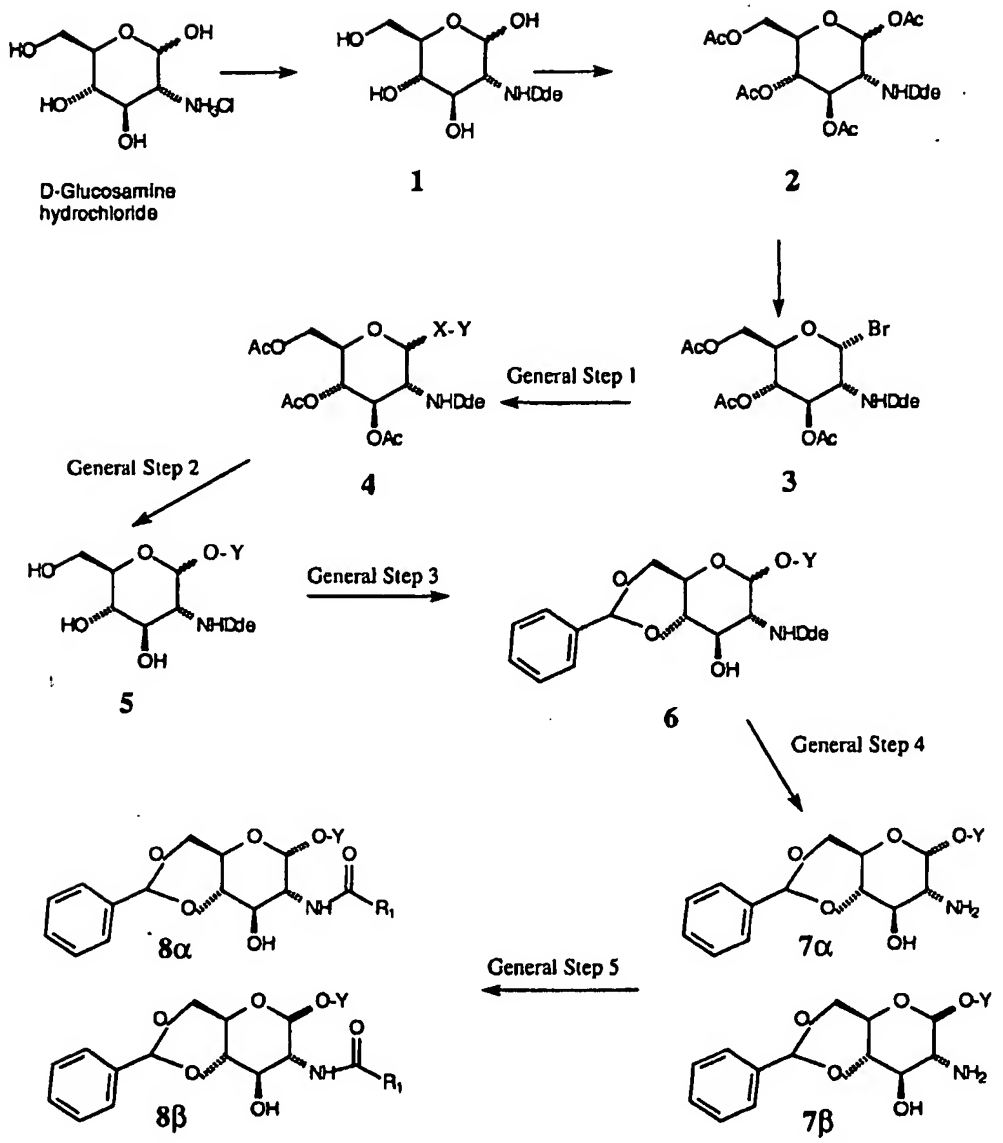
AN	Acetonitrile
MeCN	Acetonitrile

Ether	Diethyl Ether
DCM	methylene chloride; dichloromethane
MeOH	methanol
EtOAc	Ethyl Acetate
DMF	N,N-dimethylformamide
HBTU	O-benzotriaxol-1-yl-N,N,N',N'- tetramethyuronium hexafluorophosphate
TBAF	tetrabutylammonium fluoride
Dde	4,4-dimethyl-2,6-dioxocyclohex-1-ylidene
BOP	Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
PyBOP	Benzotriazol-1-yloxy-tris(pyrollidyl)phosphonium hexafluorophosphate
HATU	O-(7-Azabenzotriaxol-1-yl)-N,N,N',N'-tetramethyuronium hexafluorophosphate
Fmoc	9-Fluorenylmethylcarbamate
Boc	t-Butylcarbamate

Experimental Support

Exemplary compounds of the invention were prepared as set out in the following synthetic schemes 1 to 3 and detailed in the general procedures.

All final compounds were purified by liquid chromatography-mass spectrometry (LC-MS), using a micromass LCZ electrospray mass spectrometer as detector. Proton NMR results are included for representative compounds.



Scheme 1

y = benzyl, napthylmethyl, 2'-chloroethoxyethyl, 2''-chloroethoxyethoxyethyl.

R_1 = methyl, phenyl, ^{t}butyl, ^{t}butylmethylene, biphenyl.

2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (1)

Glucosamine hydrochloride (50g, 231mmol) was suspended in anhydrous methanol (500ml), then 2-acetyl-dimedone sodium salt (47.3g, 231mmol) was added. The reaction mixture was stirred at room temperature for 10 minutes, then 2-acetyl-dimedone (21.1g, 115.9mmol) was added. The reaction mixture was stirred under reflux for 2.5 hours and monitored by tlc. At the completion of the reaction (TLC: MeCN-H_2O, 10:2), the reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated and the resulting solid residue was washed on a funnel with ether (3 x 500 ml) and dried to give crude product (75g, 94%). No further purification was required for the next reaction.

1,2,4,6-tetra-O-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (2)

Crude 2-Deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α,β-D-glucopyranose (75g, 218.6mmol) was dissolved in pyridine (320ml) and acetic anhydride (165ml) was added dropwise keeping the temperature below 30°C. The reaction mixture was stirred overnight then solvents evaporated. Toluene (2 x 100ml) was evaporated off the residue. The residue was taken up in CH_2Cl_2 (550ml), washed with 5% HCl solution (280ml), water (3 x 1l), saturated $NaHCO_3$ (1l), then dried over magnesium sulphate and the solvents evaporated. The product was crystallised from MeOH (250ml), filtered, washed with cold MeOH (-40°C) on the funnel. The solid was dried to give 1,2,4,6-tetra-O-Acetyl-2-deoxy-2-Deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (95g, 85%).

3,4,6-tri-O-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (3)

1,2,4,6-tetra-O-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (150g, 293.5 mmol) was dissolved in dry CH_2Cl_2 (300 ml) and hydrogen bromide in acetic acid (400 ml, 30%) was added. The reaction mixture was stirred at room temperature for 2 hours, then diluted with cold CH_2Cl_2 (-15°C, 2 l) and washed with cold water (0°C, 3 times 2l), saturated $NaHCO_3$ (2 l). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* at 30°C. The resulting white solid residue was suspended in ether (1 l) and filtered. The solid was dried under vacuum giving 3,4,6-O-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohexa-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (150g, 95%).
Rf 0.62 (EtOAc / Hexane 2:1); MS (electrospray) $C_{22}H_{30}BrNO_9$ (532.1/534.0) m/z (%) 533.38/535.38 $[M + H]^+$ (100).

General Step 1: Reaction of (3) with acceptor alcohols

A mixture of 3,4,6-tri-*O*-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-β-*D*-glucopyranosyl bromide (**3**) (1 equivalent), the acceptor alcohol (1.5 equivalents) and activated [4A] molecular sieves (equal mass as bromide (**3**)) were stirred in 1,2-dichloroethane (10 ml per gram of (**3**)) under a nitrogen atmosphere at -78°C in a flask that had been covered to preclude ambient light. Silver triflate (**1.45** equivalents) was added and the mixture allowed to warm to room temperature. This reaction was then stirred at room temperature for 1 hour, diluted with CH_2Cl_2 (20 mL per gram of (**3**)) and filtered through a plug of Celite. The eluent was then washed with saturated $NaHCO_3$ (3 times 10 ml per gram of (**3**)), dried (MgSO4) and the solvent removed *in vacuo* to yield an anomeric mixture of the glycosylated compounds.

Acceptor A = 2-(2-(2-Chloroethoxy)ethoxy)ethanol, amount of (3) used 21 gm, yield 4A 20.57 gm (84%)
MS (electrospray) $C_{28}H_{42}ClNO_{12}$ (619.3/621.2) m/z (%) 620.32/622.4 $[M + H]^+$ (100).

Acceptor B = 2-(2-Chloroethoxy)ethanol,
amount of (3) used = 35 gm, yield 4B 37 gm 97%

Acceptor C = 2-napthylmethanol,
amount of (3) used 34.5 gm, yield 4C 25.75 gm (66%)
MS (electrospray) $C_{33}H_{39}NO_{10}$ (609) m/z (%) 610$[M + H]^+$ (100).

Acceptor D = Benzyl alcohol
Amount of (3) used 2.24 gm, yield 4D 2.35 gm

General Step 2: Deacylation of glycosylation products 4

Products of general step 1 (1 eq) were dissolved in methanol (4 ml per gram of substrate) and sodium metal (10 mg per gram of substrate dissolved in methanol) was added. The reaction vessel was fitted with a calcium chloride guard tube and the mixture stirred at room temperature for 30 minutes with monitoring by t.l.c (EtOAc / Hexane 2:1). When the reaction was complete Amberlite IR-120 (H) cation exchange resin was added to the mixture until slightly acidic (pH 5 - 6). The resin was filtered off and the solvent removed *in vacuo*. The residue was further purified by passing through a short column of silica gel and eluting with (acetonitrile / water 10:1). Solvents were removed to yield the desired triols 5A, 5B, and 5C

5A) Substrate 41.30 grams yield 30.98 grams (94%)
MS (electrospray) $C_{22}H_{36}ClNO_9$ (493.2,495.1) m/z (%) 494, 496 $[M + H]^+$ (30); (516.1,518.2) m/z (%) 516, 518 $[M + Na]^+$ (100).
5B) amount of substrate 4B 37 gm, Yield 28.5 gm 97%

5C) amount of substrate 4C 25.70 gm , Yield 18.24 gm (89%) MS (electrospray) $C_{27}H_{33}NO_7$ (483) m/z (%) 484 $[M + H]^+$ (100); (507) m/z (%) 507 $[M + Na]^+$ (35).

General Step 3: Benzylidene acetal formation

Product from general step 2 (5A, 5B or 5C) 1 equivalent was dissolved in dry acetonitrile (7.5 mL per gram of substrate),benzaldehyde dimethyl acetal (2 equivalents) and *para*-toluenesulfonic acid monohydrate (2 mg per gram of substrate) were added. The flask was fitted with a calcium chloride guard tube and the mixture stirred at 60°C for 14 hours, after which triethylamine (1 ml) was added and the solvent removed *in vacuo*. The residue was taken into CH_2Cl_2 (20 ml per gram of substrate) and washed with brine (3 times 5 ml per gram of substrate), dried ($MgSO_4$) and the residue triturated with ether/petrol. The solvent was then removed *in vacuo* to yield the desired acetals as a white solid. The product was used without further purification in the next step.

General Step 4: Removal of Dde

The product of general step 3 (6A to 6C) was dissolved in a mixture of methanol and aqueous ammonia (28%) 1:1 (20 ml per gram of substrate) and warmed to 60°C for 14 hours. The solvents were removed *in vacuo* and the residue purified by column chromatography (gradient acetonitrile to acetonitrile methanol 1:1) to yield both the α and β anomers as pure components.

amount of substrate Crude 5A 76.5 gm ,
Yield 7Aα 20.6 gm (38%)
yields are over 3 steps.
MS (electrospray) $C_{19}H_{28}ClNO$ (417,419) m/z (%) 418,420[M +H]$^+$ (100), 250 (70).

Yield 7Aβ 12.6 gm (23%)
MS (electrospray) $C_{19}H_{28}ClNO$ (417,419) m/z (%) 418,420[M +H]$^+$ (100).

amount of substrate pure **5B** 34.1 gm ,
Yield 7Bα 8.16 gm 34%
Yield 7Bβ 14.86 gm 62%

amount of substrate crude 5C 20.30 gm ,
Yield 7Cα 1.2 gm
yields are over 3 steps.
^{1}H NMR (500 MHz, CD_3OD) δ 7.30-8.10 (14H m aromatics + NH_2), 5.55 (1H s Ph-[CH)], ?? 5.20 (1H d J=12 napthyl CH_a), 5.00 (1H d J=12 napthyl CH_b), 4.95 (1H d J=4 H-1), 4.25 (1H dd J=5,10 H-4), 3.90-4.00 (1H m H-5), 3.75-3.80 (2H m H-6), 3.50 (1H t J=9.5 H-3), 2.80-2.85 (1H m H-2).
Yield 7Cβ 6.58 gm
MS (electrospray) $C_{24}H_{25}NO_5$ (407) m/z (%) 408 [M + H]$^+$ (100).
^{1}H NMR (500 MHz, CD_3OD) δ 7.35-8.15 (14H m aromatics + NH_2), 5.55 (1H s Ph-CH), 5.40 (1H d J=12 napthyl CH_a), 5.05 (1H d J=12 napthyl CH_b), 4.45 (1H d J=8 H-1), 4.40 (1H dd J=5,10 H-4), 3.85 (1H t J=10 H-3), 3.55-3.65 (2H m H-6), 3.45-3.5 (1H m H-5), 2.80-2.90 (1H m H-2).

General Step 5: Selective acylation of free amine

The products of general step 4 (7Aα, 7Aβ, 7Bα, 7Bβ, 7Cα, and 7Cβ) were dissolved in dry methanol (10 ml per gram of substrate) (dry dichloromethane may be substituted for methanol) and the solution stirred at room temperature. Where available the symmetrical anhydride of the acylating agent was added (1.05 equivelants). In the case of the biphenylcarbonyl, ^{t}Butylacetyl and ^{t}Butylcarbonyl acyl groups the acid chloride was used. In many cases the product began to precipitate after 5 minutes and the product was collected after 30 minutes by filtration. The solid was washed with a small amount of cold methanol. In

cases where the product did not precipitate, the product was partitioned between dichloromethane and sodium hydrogen carbonate solution. The organic layer being dried and evaporated to yield the desired product. The yields are summarized in Table 1.

Table 1

NMR data / yields for general step 5 of Scheme 1

	7Aα yield	7Aβ yield	7Aα H-1 shift	7Aβ H-1 shift
1)Acetyl	74%	89%	Not recorded	4.53 d J=8.0
2)Benzoyl	69%	82%	4.95 d J=4.0	4.71 d J=8.0
3)Biphenylcarbonyl	80%	73%	Not recorded	4.66 d J=7.0
4)^{t}Butylcarbonyl	74%	84%	Not recorded	4.75 d J=9.0
5)^{t}Butylacetyl	68%	80%	Not recorded	4.85 d J=9.0
	7Bα yield	7Bβ yield	7Bα H-1 shift	7Bβ H-1 shift
1)Acetyl	44%	86%	4.72 d J=4.0	4.77 d J=8.4
2)Benzoyl	66%	75%	Not recorded	3.86 d J=7.7
3)Biphenylcarbonyl	87%	86%	Not recorded	3.88 d J=7.8
4)^{t}Butylcarbonyl	85%	69%	Not recorded	4.87 d J=8.3
5)^{t}Butylacetyl	76%	77%	4.56 d J=3.0	4.79 d J=8.4
6)2-nitrophenacetyl	Not done	83%	Not done	Not recorded
	7Cα yield	7Cβ yield	7Cα H-1 shift	7Cβ H-1 shift
1)Acetyl	61%	87%	5.10 d J=3.0	4.85 d J=8.0
2)Benzoyl	75%	89%	Not recorded	4.90 d J=8.0
3)Biphenylcarbonyl	87%	82%	5.25 d J=4.0	4.90 d J=8.0
4)^{t}Butylcarbonyl	58%	83%	Not recorded	4.90 d J=8.0
5)^{t}Butylacetyl	68%	80%	Not recorded	4.85 d J=8.2

Expected masses were observed for each compound and 1H NMR spectra were recorded for selected compounds.

General Step 6: Alkylation of C-3 hydroxyl

The products of general step 5 (8Aα, 8Aβ, 8Bα, 8Bβ, 8Cα, and 8Cβ) with their appropriate acyl groups on nitrogen as indicated in the tables above (1 equivalent) were dried under high vacuum and added to a stirred suspension of 95% Sodium Hydride(2 equivalents) in dry N,N-dimethylformamide at 0°C under nitrogen. The mixture was stirred for 30 minutes, then the alkylating agent (methyl bromoacetate: 2 equivalents) was added and the reaction mixture allowed to warm to room temperature. The reaction was monitored by LC-MS for disappearance of starting alcohol. Typically reactions proceeded over 3 hours; however in some instances, the mixture was stirred overnight. The reaction mixture was worked up by cooling the mixture to 0°C and quenching unreacted sodium hydride with methanol. Solvents were removed *in vacuo*, and the residue taken up in dichloromethane and extracted with 10% citric acid, saturated sodium chloride then dried over anhydrous magnesium sulphate and concentrated.

In cognate preparations ^{t}Butyl bromoacetate and benzyl bromoacetate have been used as the alkylating agent.

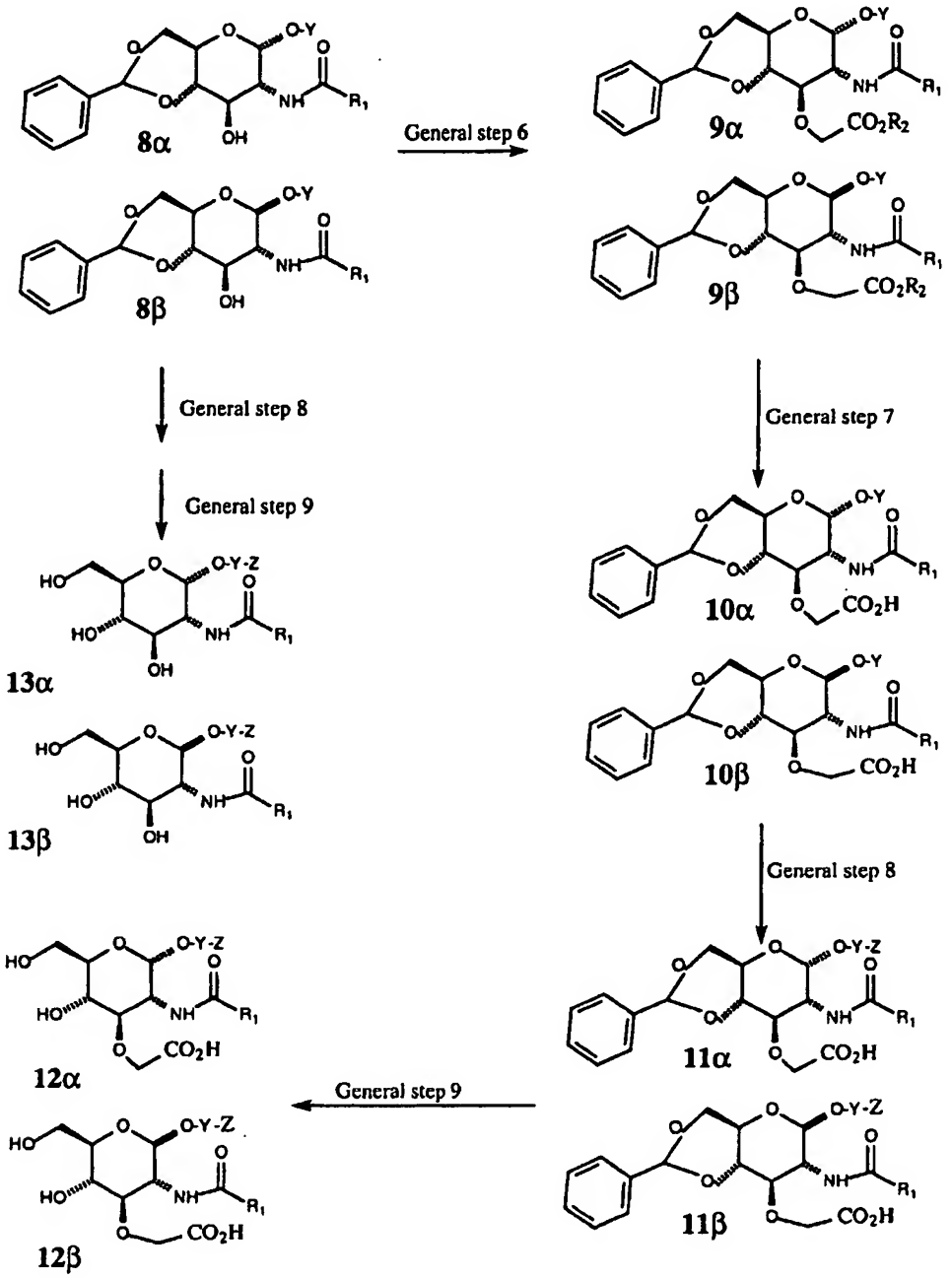
1H NMR spectra were recorded for 10 example products of this reaction. In each case a characteristic methyl singlet at δ 3.45 was observed corresponding to the methyl ester group. The location and coupling constant of the anomeric proton remained essentially unchanged.

Exemplary yield and Mass spec data are shown in the Table 2.

Table 2

MS data / yields for general step 6 of Scheme 2

Compound	Yield	M+H (%)
9Cβ acetate	76%	522 (100)
9Cβ benzoate	66%	584 (100)
9Cβ biphenylformate	82%	660 (100)
9Cβ ^{t}Butylformate	78%	564 (100)
9Cβ ^{t}Butylacetate	87%	578 (100)
9Aβ acetate	90%	532 (50)
9Aβ benzoate	78%	594 (100)
9Aβ biphenylformate	59%	670 (100)
9Aβ ^{t}Butylformate	84%	
9Aβ ^{t}Butylacetate	77%	
9Bβ acetate	88%	
9Bβ benzoate	53%	
9Bβ biphenylformate	81%	
9Bβ ^{t}Butylformate	Not recorded	
9Bβ ^{t}Butylacetate	Not recorded	
9Cα acetate	77%	522 (100)
9Cα benzoate	62%	584 (100)
9Cα biphenylformate	63%	660 (100)
9Cα ^{t}Butylformate	98%	564 (100)
9Cα ^{t}Butylacetate	44%	578 (100)
9Aα acetate	74%	532 (50)
9Aα benzoate	87%	594 (100)
9Aα biphenylformate	79%	670 (100)
9Aα ^{t}Butylformate	68%	
9Aα ^{t}Butylacetate	74%	
9Bα acetate	Not recorded	
9Bα benzoate	93%	550 (80)
9Bα biphenylformate	Not recorded	626 (100)
9Bα ^{t}Butylformate	55%	530 (70)
9Bα ^{t}Butylacetate	89%	544 (95)



Scheme 2

R_2 = methyl, benzyl, ^{t}butyl

R_1 is as defined in scheme 1 above

Y is as defined in scheme 1 above

Z is -S-(4-methoxy)phenyl; -S-(4-methyl)phenyl; -S-(4-chloro)phenyl; -S-(3,4-dichloro)phenyl; -S-(3-trifluoromethyl)phenyl

General Step 7: Ester hydrolysis

The products of general step 6 (9Aα, 9Aβ, 9Bα, 9Bβ, 9Cα, and 9Cβ) with their appropriate acyl groups on nitrogen as indicated in the tables above were hydrolysed by treatment of a solution of the ester in tetrahydrofuran/methanol (3:2, approx 10 mL per gram of substrate) with aqueous sodium hydroxide (1M, 2 equivalents). Removal of the solvents *in vacuo* yielded the sodium salt of the corresponding acid and sodium hydroxide as crude product (10Aα, 10Aβ, 10Bα, 10Bβ, 10Cα, and 10Cβ) with their appropriate acyl groups on nitrogen

General Step 8: Thiol displacement of halide

The substrate was dissolved in N,N-dimethylformamide and treated with the appropriate thiol (1.3 equivalents) which was pre-evaporated from 1.3 equivalents of sodium methoxide. 1.3 equivalents of sodium iodide was added to the solution and the mixture stirred overnight at room temperature under nitrogen. After this time, the solvents were removed *in vacuo* and the crude preparation passed through a plug of silica gel with ethyl acetate eluent, to yield essentially pure product.

Exemplary products are shown in Table 3. M+H ion and relative intensity are shown. Yields, where shown, are purified yields

Table 3

MS data / yields for general step 8 of Scheme 2

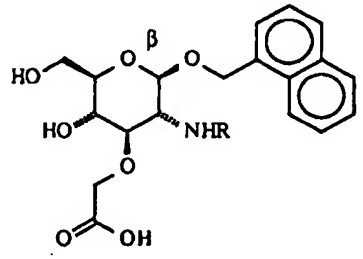
Substrate	4-methyl thiophenol	4-methoxy thiophenol	4-chloro thiophenol	3,4-dichloro thiophenol	3-trifluoromethyl thiophenol
10Aβ benzoate	668 (80)				
10Aβ acetate	606 (80)				
10Aβ biphenyl formate	744 (100)				
10Bβ acetate	562 (70)				
10Bβ biphenyl formate	700 (50)				
10Bβ benzoate	623 (65)				
8Aβ acetate	549 (10%) 53% yield	565 (10%) 91% yield	569 (15%) 89% yield	603 (3%) 64% yield	603 (3%) 80% yield
8Aβ benzoate	611 (6%) 34% yield	627 (5%) 29% yield	631 (8%) 39% yield	665 (4%) 42% yield	665 (3%) 40% yield
8Aβ biphenyl formate	quant. Yield (crude)	quant. Yield (crude)	quant. Yield (crude)	quant. Yield (crude)	quant. Yield (crude)
8Aβ ^{t}Butyl formate	591 (10%) 67% yield	607 (10%) 89% yield	611 (5%) 78% yield	646 (12%) 89% yield	645 (15%) 74% yield
8Aβ ^{t}Butyl acetate	605 (9%) 30% yield	621 (16%) 43% yield	625 (3%) 77% yield	659 (12%) 39% yield	659 (13%) 30% yield
8Aα acetate	549 (15%) 71% yield	565 (10%) 96% yield	569 (17%) 93% yield	603 (12%) 56% yield	603 (7%) 86% yield
8Aα benzoate	611 (7%) 33% yield	627 (1%) 28% yield	631 (2%) 23% yield	665 (1%) 35% yield	665 (1%) 26% yield
8Aα biphenyl formate	Not prepared	Not prepared	Not prepared	Not prepared	Not prepared
8Aα ^{t}Butyl formate	591 (11%) 45% yield	607 (17%) 46% yield	611 (15%) 46% yield	646 (13%) 47% yield	645 (27%) 47% yield
8Aα ^{t}Butyl acetate	605 (17%) 20% yield	621 (26%) 43% yield	625 (11%) 35% yield	659 (10%) 41% yield	659 (21%) 41% yield

Table 3 cont.

8Bβ acetate	504 (26%) 74% yield	520 (40%) 70% yield	524 (30%) 67% yield	558 (25%) 81% yield	558 (37%) 81% yield
8Bβ benzoate	566 (19%) 42% yield	582 (7%) 83% yield	586 (10%) 73% yield	621 (3%) 66% yield	620 (10%) 75% yield
8Bβ biphenyl formate	72% yield	75% yield	37% yield	83% yield	80% yield
8Bβ ^{t}Butyl formate	546 (20%) 79% yield	562 (10%) 97% yield	566 (10%) 97% yield	600 (4%) 71% yield	600 (11%) 73% yield
8Bβ ^{t}Butyl acetate	560 (14%) 72% yield	576 (9%) 68% yield	580 (7%) 69% yield	614 (3%) 99% yield	614 (9%) 75% yield
8Bα acetate	70% yield	50% yield	66% yield	81% yield	59% yield

General Step 9: Benzylidene cleavage

The benzylidene compounds were taken up in methanol and acetonitrile, (100 mg of compound in 1 mL of acetontirile and 2 ml methanol) and treated with amberlite IRA (H^+ form) at 45°C for 12 hours. After this time the resin was removed by filtration and the solvents evaporated *in vacuo*. The products were purified by reverse phase HPLC with mass



based detection.

Exemplary ^{1}H NMR data:

R = acetate: 7.35-8.05, m, 7H (Aromatics); 5.35,d,J=12.0, 1H (benzylic); 4.95, d, J=12.0, 1H (benzylic); 4.55, d, J=8, 1H (H-1); 3.15-4.05, m, 8H; 1.80, s, 3H (acetate CH_3).

R = benzoate: 7.10-8.35, m, 12H (Aromatics); 5.20,d,J=12.0, 1H (benzylic); 5.00, d, J=12.0, 1H (benzylic); 4.65, d, J=8, 1H (H-1); 3.20-4.20, m, 8H.

R = biphenylcarbonyl: 7.10-8.30, m, 16H (Aromatics); 5.25,d,J=12.0, 1H (benzylic); 5.00, d, J=12.0, 1H (benzylic); 4.70, d, J=8, 1H (H-1); 3.20-3.90, m, 8H.

R = ^{t}butylcarbonyl: 7.30-8.10, m, 7H (Aromatics); 5.25,d,J=12.0, 1H (benzylic); 5.00, d, J=12.0, 1H (benzylic); 4.65, d, J=8, 1H (H-1); 3.20-4.15, m, 8H; 0.95, s, 9H (^{t}butyl 3xCH_3).

Exemplary HPLC and mass spectral data products are shown in the attached figures.

Figure 1 LC-MS data for

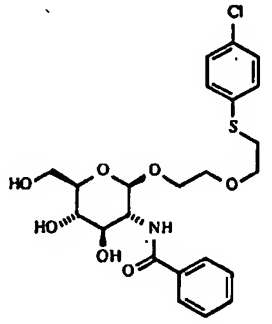


Figure 2 LC-MS data for

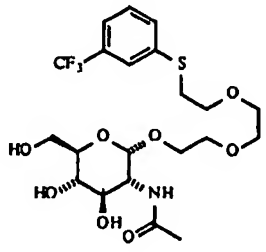
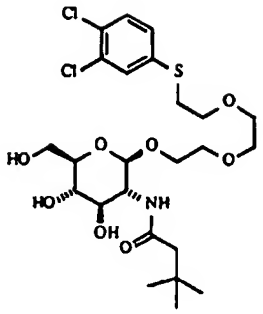


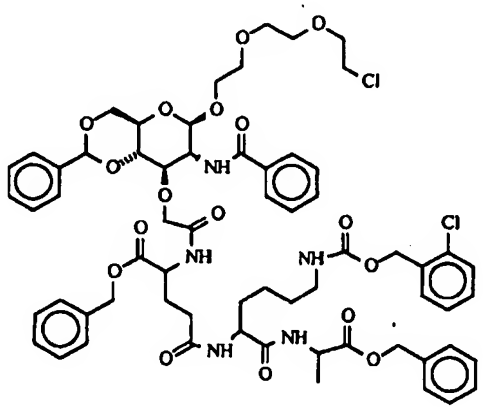
Figure 3 LC-MS data for



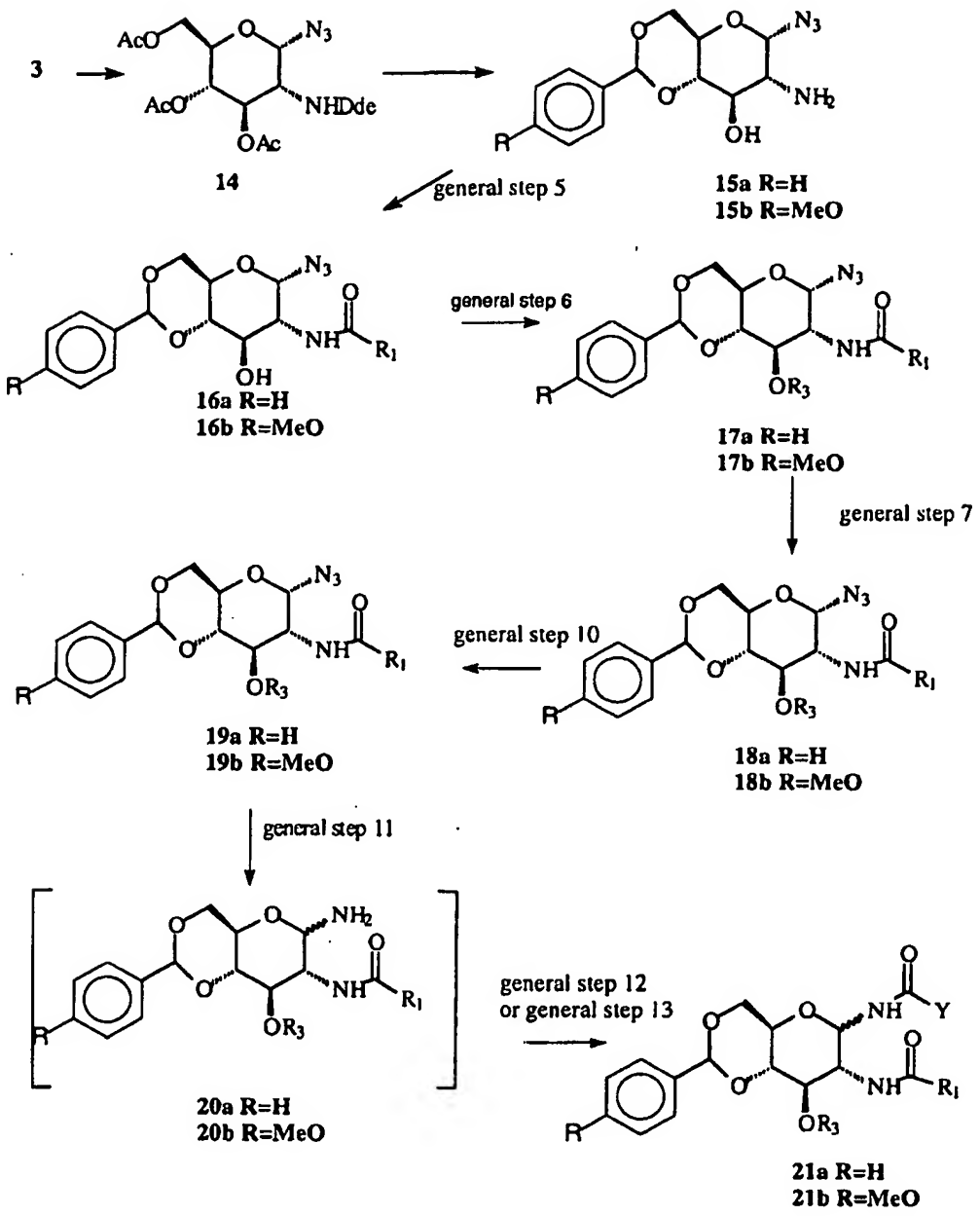
General Step 10: Coupling of groups to the C-3 acid moiety

Acid substrates (10) are dissolved in N,N-dimethylformamide and activated with HBTU in the presence of triethylamine. Peptides with one free amine, amino acids with one free amine or other nucleophillic amines are added in excess and the mixture stirred for 2 hours. After this time the solvents are removed *in vacuo* and the crude material chromatographed on silica gel to yield the desired product.

In a specific example, substrate 10Aβ benzoate was reacted with the tripeptide α-O-benzyl-γ-glutamyl-ω-(2-chlorobenzylcarbamoyl)-lysinyl-O-benzyl-alanine to yield the desired protected product. HPLC and mass spectral data are shown in Figure 4.



In this instance the benzyl and o-chloro-benzyloxycarbonyl protecting groups were removed by hydrogenolysis in methanol with 10% palladium on charcoal as catalyst (1% w/w Pd; 40 psi, 2 hours). The benzylidene was subsequently removed as described in **general step 9**. In a cognate experiment in which alanine ^{t}butyl ester was used, the ^{t}butyl protecting group and the benzylidene were removed by **general step 9**. It is expected that BOC amine protecting groups will be similarly amenable to this latter deprotection strategy.



Scheme 3

17 R_3 = -CH2-COOMe

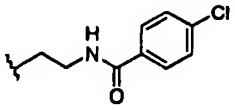
18 R_3 = -CH2-COOH

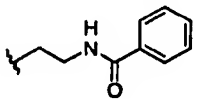
19,20,21 R_3 = -CH2-CONH-OBn ; -CH2-CONH-CH(CH3)-COOBn

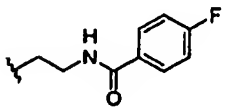
or 17, 18, 19, 20, 21 R_3 = is 2-nitrophenyl; benzyl; 4-methylbenzyl; 4-chlorobenzyl; 4-methoxybenzyl; 4-phenylbenzyl; 1- napthylmethyl; 2-napthylmethyl.

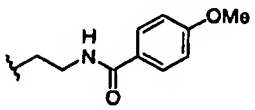
R_1 is as defined in scheme 1 + Dde; 4-methylphenyl.

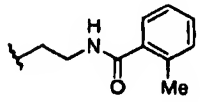
Y is shown in the following list:

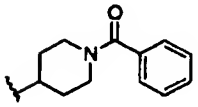
A 

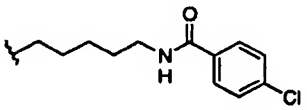
B 

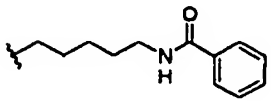
C 

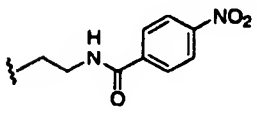
D 

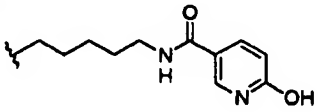
E 

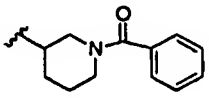
F 

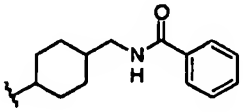
G 

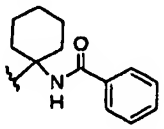
H 

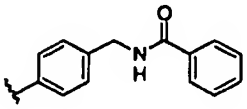
I 

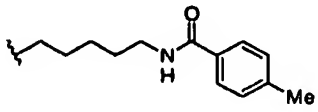
J 

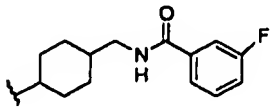
K 

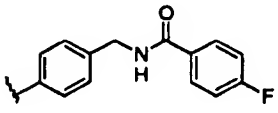
L 

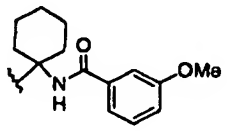
M 

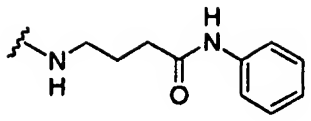
N 

O 

P 

Q 

R 



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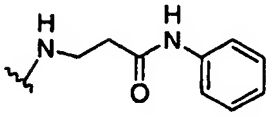

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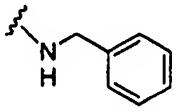


U

1-Deoxy-1-azido-3,4,6-tri-*O*-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (14):

3,4,6-tri-*O*-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (3) (60g, 0.112 mol) is suspended in acetonitrile (280mL) and trimethylsilylazide (TMS-N_3) (29.9 µL, 0.224 mol) is added dropwise followed by the dropwise addition of tetrabutylammonium fluoride (1M TBAF in tetrahydrofuran) (225 mL, 0.225 mol). The reaction is stirred for 16 hr protected from light. The solvents are removed under reduced pressure, and the residue is preabsorbed on silica (150g) and the product eluted with ethyl acetate / petroleum ether (1:1) (2 L). The solvents are evaporated and the crude residue used directly in the next step.

Alternative preparation of 1-Deoxy-1-azido-3,4,6-tri-*O*-acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranose (14):

3,4,6-tri-*O*-Acetyl-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-α-D-glucopyranosyl bromide (3) (150g, 0.282 mol) is suspended in ethyl acetate (3000mL)and a solution of 10% aqueous sodium hydrogen carbonate (1500 mL) containing sodium azide (22 g, 0.338 mol) is added. Tetrabutylammonium hydrogen sulfate (28.7g, 30 mol%) was added and the biphasic mixture stirred vigorously for 16h. The organic layer was then separated, extracted and dried, then the solvent removed at reduced pressure. The residue was chromatographed as above to yield the desired product (105g, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 13.90 (d, J=9.6, 1H), 5.22 (t, J=9.6, 1H), 5.11 (t, J=9.7, 1H), 4.90 (d, J=8.9, 1H), 4.36 (dd, J=4.5, 12.5, 1H), 4.17 (dd, J=12.4, 1.7, 1H), 3.81-3.91 (m, 2H), 2.60 (s, 3H), 2.42 (s, 2H), 2.36 (s, 2H), 2.11, (s, 3H), 2.04 (s, 3H), 1.03 (s, 3H)

m/z 495 (M+H).

1-Deoxy-1-azido-2-deoxy-2-amino-4,6-benzylidene-α-D-glucopyranose (15a) :

The crude product **14** is taken up in methanol (450 mL) and sodium metal (2.5g, 0.112 mol) added carefully. The reaction vessel is guarded from the light and stirred for 45 minutes. The reaction is neutralized to pH 6 with Amberlite IR 120(H) resin. The resin is filtered and solvents evaporated under reduced pressure at rt. The residue is adsorbed on silica (150 g) and the product washed out with acetonitrile/water (1:1) (1L). Solvents are evaporated under reduced pressure (at rt). Remaining water is removed by adding acetonitrile and evaporating under reduced pressure. The crude reaction product is suspended in acetonitrile (dry, 450 mL) and benzaldehyde dimethyl acetale (34.3g, 0.225mol) and *para*-toluenesulfonic acid monohydrate (0.4g, 0.225mol) were added. The reaction mixture is heated to 80C for 2 hours, then triethylamine (1 equivalent) added and solvents evaporated under reduced pressure. The residue is adsorbed on silica (150g) and the

silica washed with petroleum ether (500 mL). The product is eluted with ethyl acetate/petroleum ether (2/3). After evaporation of the solvents 42,73 g of crude product are obtained (83% yield from the bromo sugar 3). The product is then suspended in MeOH (475mL) and hydrazine hydrate (13.6g, 0.25mol) added at 0C. The solution is stirred for 10 minutes and then another 90 minutes at rt. The volume is reduced under vacuum to half, ethyl acetate (200 mL) is added and the organic solution washed with brine. The organic layer is dried on magnesium sulfate and evaporated to dryness. The residue is adsorbed on silica (100 g) and eluted with ethyl acetate/petroleum ether (3/2) (400 mL)then with ethyl acetate (400 mL) and finally with acetonitrile / ethyl acetate (1/5). The product is separated as a white solid (20.31 g,74%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 - 7.53 (5H m aromatics), 5.54 (1H, S, Ph-CH) 4.53 (1H, d, J=8.8, H-1), 4.3-4.4 (1H,m), 3.7-3.8 (1H, m), 3.4-3.6 (3H, m), 2.71 (1H, t, J=9, H-3), 1.62 (2H, br).

Cognate preparation of 1-Deoxy-1-azido-2-deoxy-2-amino-4,6-p-methoxybenzylidene-α-D-glucopyranose (15b) :

This compound was prepared in an analogous manner to 15a except that 4-methoxybenzaldehyde dimethyl acetal was used in place of benzaldehyde dimethyl acetal.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J=10, 2H), 6.89 (d, J=10, 2H), 5.51 (1H, S) 4.54 (d, J=8.8,1H), 4.35 (dd, J=4.2, 10.5, 1H), 3.80 (s, 1H), 3.74-3.90 (m, 1H), 3.57 - 3.63 (m, 1H),3.50 -3.55 (m, 2H), 2.71(1H, t, J=9.1, 1H. m/z 323.18 (M+H)

General step 5 to N-acylate (16a):

Example :**1-Deoxy-1-azido-2-deoxy-2-*N*-(acetyl)-amino-4,6-benzylidene-α-D-glucopyranose:** the product is isolated in 97% yield (2.22g, 6.6 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ□7.26-7.52 (5H, m, aromatics), 5.56 (1H, S, Ph-CH), 4,83 (1H, d, J=9.3), 4.75 (1H, d,

J=4.5), 4.3-4.4 (1H, m), 3.9-4 (1H,m), 3.7-3.8(1H, m), 3.6-3.7 (1H, m), 3.5 -3.6 (2H, m), 2.0 (3H)

General step 5 to N-acylate (16b):

Example: 1-Deoxy-1-azido-2-deoxy-2-*N*-(acetyl)-amino-4,6-p-methoxybenzylidene-α-D-glucopyranose:

Was prepared by general method 5 utilising the symmetric anhydride (acetic anhydride).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J=8.5, 2H), 6.90 (d, J=7, 2H), 5.51 (1H, S) 5.01 (d, J=9.5,1H), 4.36 (dd, J=5, 10.5, 1H), 4.18 (t,J=10.0 1H), 3.81 (s, 3H), 3.78 (t, J=10.0 1H), 3.59 (dd, J=5, 9.5, 1H),3.54 (dd, J=9, 19, 1H), 3.46(dd, J=8.5,18, 1H), 2.07 (s, 3H).

m/z 365.3 (M+H)

Example: 1-Deoxy-1-azido-2-deoxy-2-*N*-(benzoyl)-amino-4,6-p-methoxybenzylidene-α-D-glucopyranose:

Was prepared by general method 5 utilising the acid chloride (benzoyl chloride).

M/z 427.3 (M+H)

Example: 1-Deoxy-1-azido-2-deoxy-2-*N*-(^{t}butylcarbonyl)-amino-4,6-p-methoxybenzylidene-α-D-glucopyranose:

Was prepared by general method 5 utilising the acid chloride (2,2,2-trimethylacetyl chloride).

M/z 407.4 (M+H)

General step 6 to prepare (17a):

Example: **1-Deoxy-1-azido-2-deoxy-2-*N*-(acetyl)-amino-4,6-benzylidene-3-(methyl acetate)-α-D-glucopyranose:** Methyl bromoacetate was employed as the alkylating agent. The target product was isolated in 74% yield (1.97gr). ^{1}H NMR (500 MHz, $CDCl_3$) δ□7.32-7.47 (5H, m, aromatics), 6.73 (1H, d, J=6.6), 5.55 (1H, s), 4.75 (1H, d, J=9.1), 4.3-4.5 (3H, m), 3.6-3.9 (7H,m), 3.5-3.6(1H, m), 2.1 (3H, s).

General step 6 to prepare (17b):

Example: **1-Deoxy-1-azido-2-deoxy-2-*N*-(acetyl)-amino-4,6-p-methoxybenzylidene-3-(methyl acetate)-α-D-glucopyranose:** Methyl bromoacetate was employed as the alkylating agent. The target product was isolated in 85% yield.
M/z 437.36 (M+H)

Example: **1-Deoxy-1-azido-2-deoxy-2-*N*-(benzoyl)-amino-4,6-p-methoxybenzylidene-3-(methyl acetate)-α-D-glucopyranose:** Methyl bromoacetate was employed as the alkylating agent. The target product was isolated in 85% yield.
M/z 499.4 (M+H)

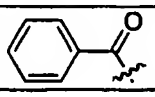
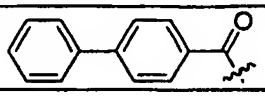
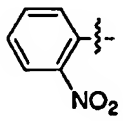
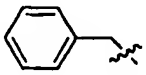
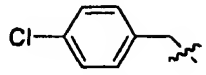
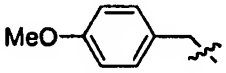
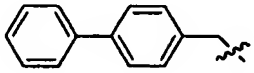
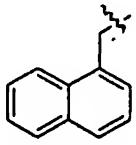
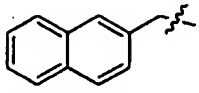
Example: **1-Deoxy-1-azido-2-deoxy-2-*N*-(^{t}butylacetyl)-amino-4,6-p-methoxybenzylidene-3-(methyl acetate)-α-D-glucopyranose:** Methyl bromoacetate was employed as the alkylating agent. The target product was isolated in 85% yield.
M/z 479.4 (M+H)

Example: **Preparation of further C-3 alkylated compounds:** The appropriate alkyl halide was employed in place of methyl bromoacetate as the alkylating agent. The target product was isolated and yields are shown in parentheses.

Table 4

MS data / yields for general step 6 Scheme 3 compounds 17b

Table of building blocks, MH+ values in ESMS and yields between brackets.

R3↓ \ R1→	Dde	CH3-CO		
	609	485 (61%)	547 (40%)	623 (68%)
	577	455 (84%)	517 (80%)	593 (100%)
	591	469 (51%)	531 (55%)	607 (63%)
	611	489 (87%)	551 (89%)	627 (97%)
	607	485 (50%)	547 (80%)	623 (95%)
	653	531 (75%)	593 (78%)	669 (91%)
	627	505 (80%)	567 (86%)	643 (100%)
	627	505 (100%)	567 (77%)	643 (86%)

General step 10 to prepare (19b): Where R_3 is other than -CH2-COOMe, this step is omitted.

Example: The products of hydrolysis of 17b were coupled according to general step 10 with L-alanine-O-benzyl ester to yield compounds of general formula 19b.

N-acetylated compound m/z 584.4 (M+H)

N-benzoylated compound m/z 646.5 (M+H)

In a cognate preparation, hydroxylamine-O-benzyl ether was coupled to the products of hydrolysis of 17b.

General step 11: reduction of the azide with Pd/C or with dithiol to prepare (20a and 20b)

1. With Pd/C: starting material (0.74 mmol) is dissolved in dichloromethane (10 mL), catalyst (Pd/C, 150 mg) is added and the solution degassed. The reaction mixture is hydrogenated (H_2 at 1 atm) for 1 hour, then filtered and solvent evaporated under reduced pressure. The crude 1-amino glycoside is employed without further purification. Example: **1-Deoxy-1-amino-2-deoxy-2-*N*-(acetyl)-amino-4,6-benzylidene-3-(methyl acetate)-α-D-glucopyranose:** product was isolated in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ□7.33-7.50 (5H, m, aromatics), 5.56 (1H, s), 4.47 - 4.55 (1H, m), 4.27-4.46 (2H, m), 4.15 (1H, d, J=9), 3.60-3.83 (7H,m), 3.37-3.44(1H, m), 2.08 (3H, s).

2. With dithiol: starting material (0.12 mmol) is dissolved in chloroform/methanol (1/1) (1.2 mL), dithiotreitol (57 mg, 3 equiv) is added and the solution degassed using a nitrogen stream. The reaction mixture is stirred under nitrogen for 10 hours. The reaction mixture is dilited with chloroform washed with water and brine, dried with magnesium sulfate and solvent evaporated. The crude 1-amino glycoside is employed without further purification for the generation for the isocyanate.

General step 12: formation of a urea bond 21a and 21b

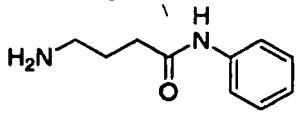
The Y substituents are introduced by reacting of *in situ* generated isocyanate (from the 1-aminopyranose **20a or 20b**) with the amino functionality of the Y group.

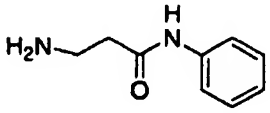
The 1-isocyanato pyranose is first generated by treating the 1-aminopyranose **20** with one equivalent of one of the following reagents: phosgene, triphosgene, 1,1'-carbonyldiimidazole, or *N,N'*-disuccinimidyl carbonate. Suitable solvents for this purpose are dichloromethane,

dimethylformamide or chloroform. The Y group is then added directly (1 equivalent) to the crude isocyanate mixture and the reaction is left stirring for 16 hours. 1 equivalent of diisopropylethylamine is added if the reaction is not complete after this time. The reaction is worked up by evaporating the solvents, adding dichloromethane and filtering the precipitated product.

The Y groups are prepared using commonly used amide bond forming procedures or urea bond forming procedures from commercially available precursors. Examples of suitable amide bond forming reagents include HBTU, BOP, HATU, and PyBOP. The urea bond in some of the Y groups are generated through the reaction of an isocyanate and an amine using well known procedures. The isocyanates are generated as above for the sugar isocyanate.

Y group reagents for general step 12 are in table 5:





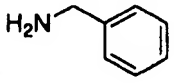


Table 5

Where Y = benzylamine m/z 514.52 M+H RT 8.55 minutes

1H nmr: (CDCl2) 1.83 (s, 3H) 3.45 (s, 3H) 3.30-4.30 (m 10H) 4.92 (dd, J=10Hz, 1Hz, 1H) 5.60 (s, 1H), 6.45 (d J=10Hz, 1H), 6.85 (t, J=6 Hz, 1H) 7.20-7.45 (m 10H), 8.20 (d J=9 Hz, 1H).

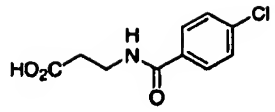
General step 13 : formation of an amide bond 21a and 21b

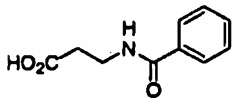
The Y substituents are introduced through an amide bond forming reaction between the 1-amino pyranose **20** and

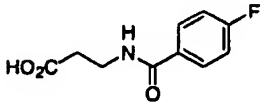
the carboxylic acid functionality on the Y group. The amine (20) (0.2 mmol) is suspended in anhydrous DMF (1.2 mL) and a solution of the appropriate acid (0.95 equiv), HBTU (87 mg, 1.15 equiv), diisopropylamine (62 mg, 83 µL, 2.4 equiv) in DMF (0.8 mL) was added. The mixture was stirred for 16 hours and the solution then diluted with chloroform (10 mL), extracted with 10% citric acid solution, dried and solvents removed to yield the desired amides (21) in yields varying from 40% to 90%.

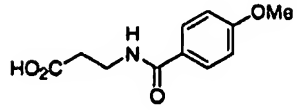
Y group reagents (carboxylic acids) for general step 13 are shown in table 6:

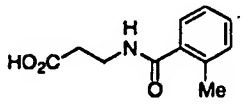
Table 6

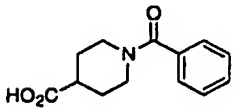
A 

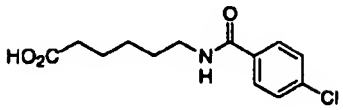
B 

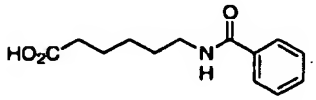
C 

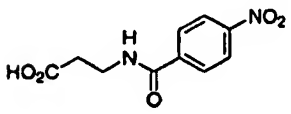
D 

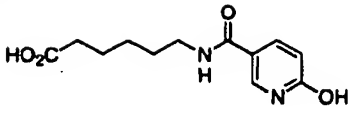
E 

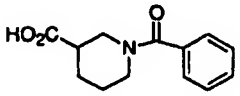
F 

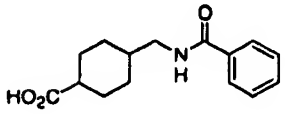
G 

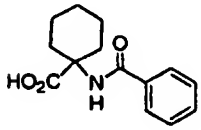
H 

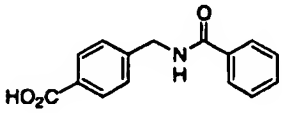
I 

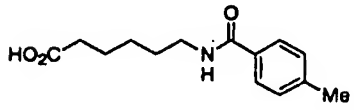
J 

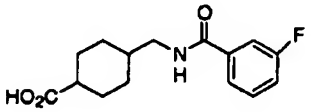
K 

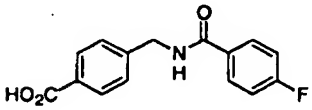
L 

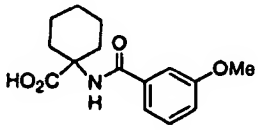
M 

N 

O 

P 

Q 

R 

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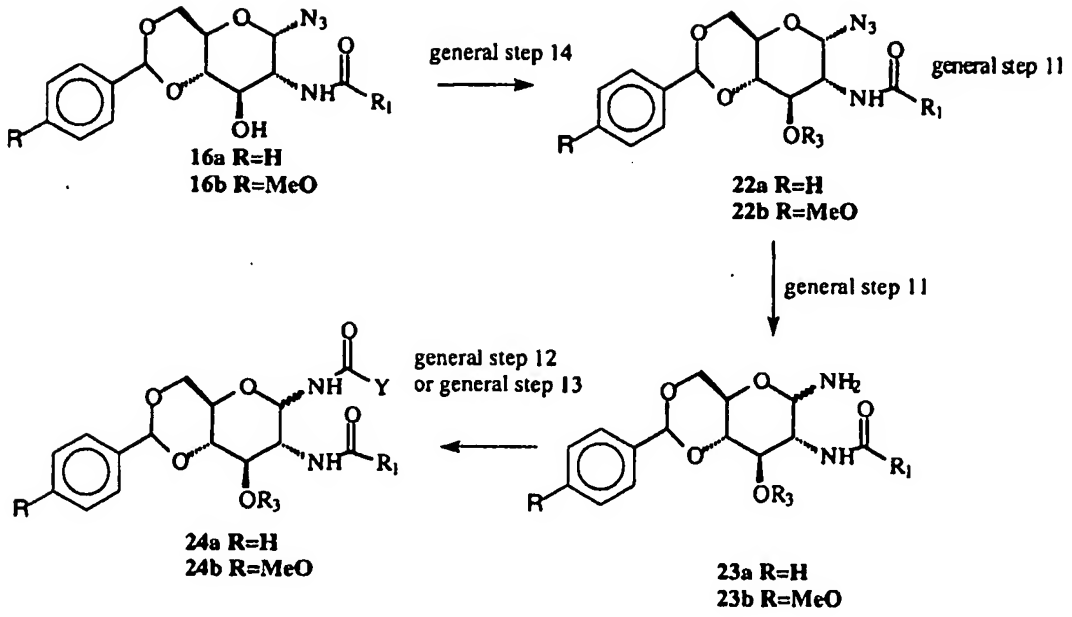

Scheme 4

R^1 is as defined in scheme 3

R_3 is acetyl; 4-chlorobenzoyl

Y is as defined in scheme 3

Acyl protection of compounds 16a and 16b to form 22a and 22b. General step 14

Compound 16 (0.27 mmol) was dissolved in DMF (1.4 ml) and diisopropylethylamine (71 mg, 96 µl, 2 equiv) added. Acetic anhydride (56 mg, 52 µl, 2 equiv) was added followed by a catalytic amount of DMAP. The mixture was stirred for 16 h, water added and stirring continued for a further 30 min. The mixture was diluted with chloroform, washed with 10% citric acid, $NaHCO_3$ solution, brine, dried ($MgSO_4$) and evaporated to give the desired compound as a white solid (85 - 95%).

In a cognate preparation 4-chlorobenzoyl chloride was used in place of acetic anhydride.

Example: **1-Deoxy-1-azido-2-deoxy-2-*N*-(acetyl)-amino-3-p-chlorobenzoyl-4,6-p-methoxybenzylidene-α-D-glucopyranose**

^1H nmr (d6-DMSO, 500 MHz)

1.91 (s, 3 H), 3.71 (dt, J = 7, 10 Hz, 1 H), 3.76 (s, 3 H), 3.84 (t, J = 10 Hz, 1 H), 3.92 (t, J = 9.5 Hz, 1 H), 4.12

(dd, J = 9.5, 19 Hz, 1 H), 4.30 (dd, J = 9.5, 10 Hz, 1 H), 5.07 (d, J = 9.5 Hz, 1 H), 5.32 (t, J = 10 Hz, 1 H), 5.63 (s, 1 H), 6.93 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.59 (d, J = 8.5 Hz, 2 H), 7.78 (d, J = 8.5 Hz, 2 H), 8.73 (d, J = 9 Hz, 1 H)

Compounds of the type 21a, 21b, 24a and 24b were further elaborated by deprotection of ester groups as exemplified by general procedure 7 followed by cleavage of the benzylidene protecting groups according to general procedure 9 to yield the final compounds as exemplified by table 7.

Compounds were analysed by HPLC/MS with evaporative light scattering detection. Retention times and peak purities for the peaks corresponding to the desired compound as detected by mass spectrometry are shown. NA denotes prepared but not analysed. Codes for Y are as shown in table 6 above.

Table 7

Number	Y	R1	R3	Retention Time	Purity % ELS (area)
1	B	Me	CH2CO2Me	1.82	77.7
2	H	Me	CH2CO2Me	2.9	78.3
3	G	Me	CH2CO2Me	3.4	51.2
4	B	Phe	CH2CO2Me	3.35	49.1
5	B	tBu	CH2CO2Me	3.28	15.9
6	B	Me	H	1.25	66.0
7	H	Me	H	2.73	99.3
8	A	tBu	H	3.51	82.1
9	H	tBu	H	3.38	85.0
10	G	tBu	H	3.75	86.4
11	H	Me	CH2CO2H	2.92	80.9
12	G	Me	CH2CO2H	3.43	83.0
13	A	Phe	CH2CO2H	3.69	70.5
14	H	Phe	CH2CO2H	3.6	88.9
15	A	Me	CH2CO2H	3.06	87.9
16	C	Me	CH2CO2Me	2.51	86.9

17	F	Me	CH2CO2Me	2.65	86.5
18	J	Me	CH2CO2Me	1.36	53.7
19	D	Me	CH2CO2Me	2.57	83.2
20	C	Phe	CH2CO2Me	3.46	92.9
21	F	Phe	CH2CO2Me	3.45	51.8
22	F	Phe	CH2CO2Me	3.69	45.1
23	J	Phe	CH2CO2Me	2.99	69.1
24	D	Phe	CH2CO2Me	3.41	73.6
25	C	tBu	CH2CO2Me	3.4	58.3
26	F	tBu	CH2CO2Me	3.38	55.5
27	J	tBu	CH2CO2Me	2.96	29.5
28	D	tBu	CH2CO2Me	3.35	62.3
29	E	Me	CH2CO2Me	2.18	81.5
30	E	Phe	CH2CO2Me	3.43	89.2
31	E	tBu	CH2CO2Me	3.34	23.4
32	C	Me	H	1.88	95.2
33	F	Me	H	2.19	95.1
34	D	Me	H	2.03	73.1
35	F	Phe	H	4.2	0.5
36	C	tBu	H	3.23	89.0
37	F	tBu	H	3.26	86.1
38	J	tBu	H	2.64	85.3
39	D	tBu	H	3.2	88.2
40	E	Me	H	1.5	95.0
41	E	tBu	H	3.17	90.5
42	B	Me	CH2CO2H	2.5	84.9
43	J	Me	CH2CO2H	0.91	72.3
44	D	Me	CH2CO2H	2.57	82.8
45	C	Phe	CH2CO2H	3.48	87.1
46	F	Phe	CH2CO2H	3.51	97.7
47	J	Phe	CH2CO2H	2.87	74.4
48	D	Phe	CH2CO2H	3.44	89.2
49	C	tBu	CH2CO2H	3.41	96.0
50	F	tBu	CH2CO2H	3.4	96.3
51	J	tBu	CH2CO2H	2.83	38.1
52	D	tBu	CH2CO2H	3.37	95.6

53	E	Me	CH2CO2H	2.22	83.0
54	E	Phe	CH2CO2H	3.43	83.1
55	K	Me	CH2CO2Me	2.88	33.2
56	L	Me	CH2CO2Me	3.07	37.1
57	N	Me	CH2CO2Me	3.16	54.0
58	O	Me	CH2CO2Me	3.26	66.2
59	P	Me	CH2CO2Me	3.26	61.4
60	I	Me	CH2CO2Me	2.74	55.9
61	Q	Me	CH2CO2Me	3.3	46.5
62	K	Phe	CH2CO2Me	3.61	90.4
63	O	Phe	CH2CO2Me	3.81	86.8
64	I	Phe	CH2CO2Me	3.52	87.1
65	A	Me	CH2CONHCH(CH3)CO2Bn	4.09	85.8
66	C	Me	CH2CONHCH(CH3)CO2Bn	3.93	88.6
67	D	Me	CH2CONHCH(CH3)CO2Bn	3.95	89.1
68	F	Me	CH2CONHCH(CH3)CO2Bn	3.89	86.0
69	G	Me	CH2CONHCH(CH3)CO2Bn	4.38	85.4
70	K	Me	CH2CONHCH(CH3)CO2Bn	3.93	86.3
71	I	Me	CH2CONHCH(CH3)CO2Bn	3.98	80.2
72	Q	Me	CH2CONHCH(CH3)CO2Bn	4.31	86.2
73	Q	Phe	CH2CO2Me	3.92	98.5
74	A	*p*MePhe	H	4.00	30.7
75	C	*p*MePhe	H	3.77	54.5
76	F	*p*MePhe	H	3.75	64.0
77	K	*p*MePhe	H	3.91	84.5
78	M	*p*MePhe	H	4.85	2.1
79	L	Me	CH2CO2H	3.07	92.5
80	N	Me	CH2CO2H	3.15	59.9
81	O	Me	CH2CO2H	3.26	72.4
82	P	Me	CH2CO2H	3.25	69.4
83	I	Me	CH2CO2H	2.75	50.4
84	Q	Me	CH2CO2H	3.32	54.7
85	R	Me	CH2CO2H	4.32	79.2
86	K	Phe	CH2CO2H	3.61	80.7
87	I	Phe	CH2CO2H	3.53	88.2
88	A	Me	CH2CONHCH(CH3)CO2H	2.66	18.5

89	C	Me	CH2CONHCH(CH3)CO2H	2.87	69.4
90	D	Me	CH2CONHCH(CH3)CO2H	2.60	1.7
91	G	Me	CH2CONHCH(CH3)CO2H	3.50	51.8
92	H	Me	CH2CONHCH(CH3)CO2H	3.07	81.0
93	L	Me	CH2CONHCH(CH3)CO2H	3.17	52.5
94	M	Me	CH2CONHCH(CH3)CO2H	3.34	83.7
95	I	Me	CH2CONHCH(CH3)CO2H	2.97	64.3
96	Q	Me	CH2CONHCH(CH3)CO2H	3.38	24.4
97	C	Phe	CH2CONHCH(CH3)CO2Bn	4.58	93.0
98	E	Phe	CH2CONHCH(CH3)CO2Bn	4.53	87.1
99	F	Phe	CH2CONHCH(CH3)CO2Bn	4.49	91.8
100	G	Phe	CH2CONHCH(CH3)CO2Bn	5.66	74.6
101	H	Phe	CH2CONHCH(CH3)CO2Bn	4.71	87.2
102	J	Phe	CH2CONHCH(CH3)CO2Bn	3.85	95.2
103	K	Phe	CH2CONHCH(CH3)CO2Bn	4.65 & 4.78	74.4
104	N	Phe	CH2CONHCH(CH3)CO2Bn	5.25	87.5
105	P	Phe	CH2CONHCH(CH3)CO2Bn	5.35	55.8
106	I	Phe	CH2CONHCH(CH3)CO2Bn	4.67	26.4
107	Q	Phe	CH2CONHCH(CH3)CO2Bn	5.64	81.7
108	B	Me	CH2CONHOBn	1.82	26.5
109	C	Me	CH2CONHOBn	2.55	39.1
110	D	Me	CH2CONHOBn	2.58	35.1
111	E	Me	CH2CONHOBn	2.22	16.5
112	F	Me	CH2CONHOBn	2.67	35.9
113	G	Me	CH2CONHOBn	3.98	50.6
114	H	Me	CH2CONHOBn	2.92	29.4
115	J	Me	CH2CONHOBn	3.01	25.7
116	N	Me	CH2CONHOBn	3.83	72.5
117	A	Phe	CH2CONHOBn	3.70	66.2
118	C	Phe	CH2CONHOBn	3.50	44.1
119	D	Phe	CH2CONHOBn	4.01	50.8
120	F	Phe	CH2CONHOBn	4.05	56.9
121	G	Phe	CH2CONHOBn	3.92	80.1
122	H	Phe	CH2CONHOBn	3.57	77.3
123	K	Phe	CH2CONHOBn	3.60	48.4
124	L	Phe	CH2CONHOBn	3.71	72.5

125	P	Phe	CH2CONHOBn	3.84	77.4
126	Q	Phe	CH2CONHOBn	3.91	57.8
127	A	Phe	CH2CONHCH(CH3)CO2H	3.72	36.6
128	E	Phe	CH2CONHCH(CH3)CO2H	3.47	87.2
129	F	Phe	CH2CONHCH(CH3)CO2H	3.48	92.4
130	G	Phe	CH2CONHCH(CH3)CO2H	0.00	0.0
131	H	Phe	CH2CONHCH(CH3)CO2H	3.61	92.1
132	J	Phe	CH2CONHCH(CH3)CO2H	2.90	91.4
133	K	Phe	CH2CONHCH(CH3)CO2H	4.65 & 4.80	74.7
134	L	Phe	CH2CONHCH(CH3)CO2H	3.70	93.9
135	N	Phe	CH2CONHCH(CH3)CO2H	3.77	94.8
136	P	Phe	CH2CONHCH(CH3)CO2H	3.84	87.3
137	I	Phe	CH2CONHCH(CH3)CO2H	3.53	55.0
138	B	*t*Bu	CH2CO2H	NA	NA
139	A	*t*Bu	CH2CO2H	NA	NA
140	H	*t*Bu	CH2CO2H	NA	NA
141	F	CH3	CH2CO2H	NA	NA
142	M	CH3	CH2CO2Me	NA	NA
143	R	CH3	CH2CO2Me	NA	NA
144	H	CH3	CH2CONHCH(CH3)CO2Bn	NA	NA
145	L	CH3	CH2CONHCH(CH3)CO2Bn	NA	NA
146	P	CH3	CH2CONHCH(CH3)CO2Bn	NA	NA
147	J	*p*ClPhe	H	NA	NA
148	R	*p*ClPhe	H	NA	NA
149	D	*p*MePhe	H	NA	NA
150	H	*p*MePhe	H	NA	NA
151	P	*p*MePhe	H	NA	NA
152	I	*p*MePhe	H	NA	NA
153	Q	*p*MePhe	H	NA	NA
154	K	CH3	CH2CO2H	NA	NA
155	M	CH3	CH2CO2H	NA	NA
156	L	Phe	CH2CONHCH(CH3)CO2Bn	NA	NA
157	M	Phe	CH2CONHCH(CH3)CO2Bn	NA	NA
158	B	Phe	H	NA	NA
159	H	Phe	H	NA	NA

160	G	Phe	H	NA	NA
161	C	Phe	H	NA	NA
162	E	Phe	H	NA	NA
163	D	Phe	H	NA	NA
164	A	Phe	H	NA	NA
165	B	Phe	H	NA	NA
166	H	Phe	H	NA	NA
167	G	Phe	H	NA	NA
168	C	Phe	H	NA	NA
169	E	Phe	H	NA	NA
170	D	Phe	H	NA	NA
171	A	Phe	H	NA	NA
172	K	pClPhe	H	NA	NA
173	O	pClPhe	H	NA	NA
174	I	pClPhe	H	NA	NA
175	B	pClPhe	H	NA	NA
176	H	pClPhe	H	NA	NA
177	G	pClPhe	H	NA	NA
178	C	pClPhe	H	NA	NA
179	F	pClPhe	H	NA	NA
180	E	pClPhe	H	NA	NA
181	D	pClPhe	H	NA	NA
182	A	pClPhe	H	NA	NA
183	K	pClPhe	H	NA	NA
184	O	pClPhe	H	NA	NA
185	I	pClPhe	H	NA	NA
186	B	pClPhe	H	NA	NA
187	H	pClPhe	H	NA	NA
188	G	pClPhe	H	NA	NA
189	C	pClPhe	H	NA	NA
190	F	pClPhe	H	NA	NA
191	E	pClPhe	H	NA	NA
192	D	pClPhe	H	NA	NA
193	A	pClPhe	H	NA	NA
194	L	pMePhe	H	NA	NA
195	O	pMePhe	H	NA	NA

196	R	pMePhe	H	NA	NA
197	B	pMePhe	H	NA	NA
198	G	pMePhe	H	NA	NA
199	E	pMePhe	H	NA	NA
200	L	pMePhe	H	NA	NA
201	O	pMePhe	H	NA	NA
202	R	pMePhe	H	NA	NA
203	B	pMePhe	H	NA	NA
204	G	pMePhe	H	NA	NA
205	E	pMePhe	H	NA	NA

Preparation of sulfonamide derivative 25.

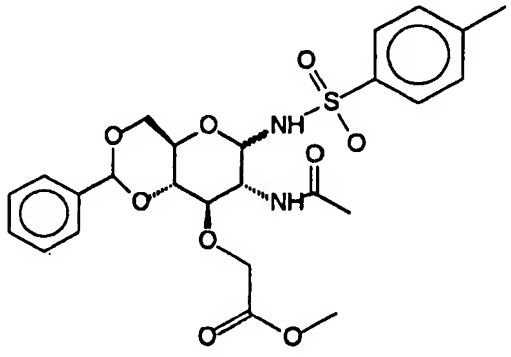

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figure 5

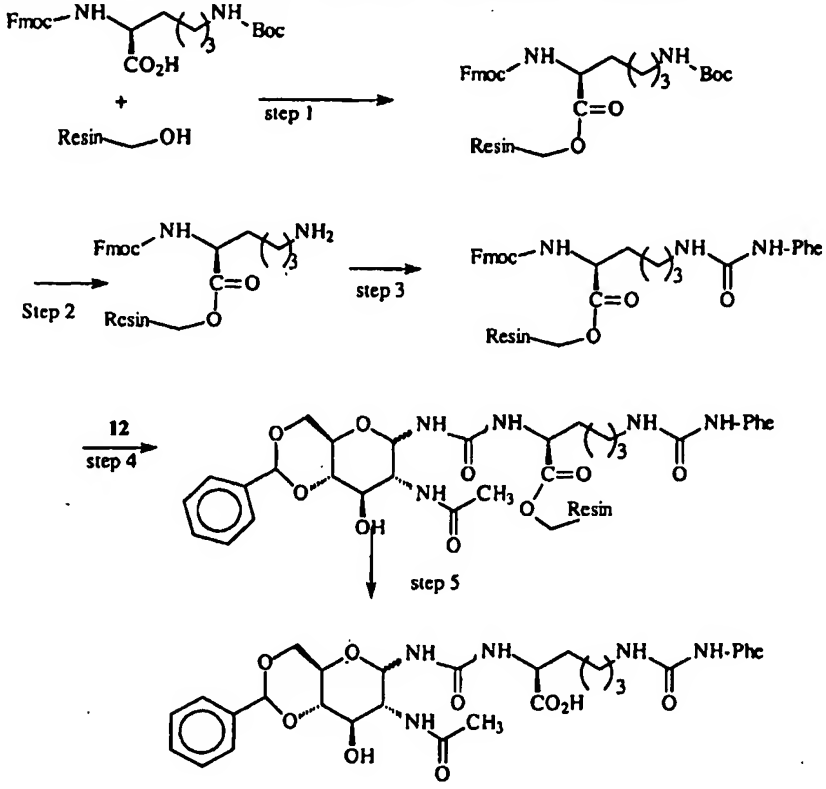
Compound 19a (40 mg)in which R1 is methyl and R3 is -CH2COOMe was dissolved in dichloromethane (1 mL), to which was added triethylamine (13 mg, 1.2 equiv) followed by p-toluenesulfonyl chloride (24 mg, 1.2 equiv). The reaction was stirred at room temperature for 18 hours, diluted with dichloromethane and extracted with 10% citric acid, saturated sodium hydrogen carbonate and brine, dried over magnesium sulfate and the solvents removed *in vacuo* to yield 25 (figure 5) (33 mg, 59 %).

Solid phase approach:

The groups may be attached to a solid support via an ester linking bond (R_6 or R_9= resin-CH_2-CO-). These resin

bound groups are prepared by linking alpha amino, alpha-hydroxy, or alphathiohydroxy acids to a commercially available hydroxy or chloromethylated resin. Suitable examples include but are not limiteds to tentagel-OH, hydroxymethyl polystyrene, Novasyn TG-hydroxy resin, or chloromethylated polystyrene.

Exemplary compounds were synthesized on solid support as described by the following reaction scheme 5:



Scheme 5

Example solid phase strategy

Solid Phase Step 1: Attachment to hydroxy-resin

Novasyn TG-hydroxy resin (purchased from Novabiochem) (1 g , 0.37 mmol/gr) is mixed with DMF (6mL), left standing for 30 min. and then filtered off. Fmoc-L-Lysine(Boc)-OH (940 mg, 2 mmol) is dissolved in dichloromethane (4 mL) at 0C and dicyclohexylcarbodiimide (206 mg, 1mmol) is added at once. After 20 minutes the DCM is evaporated, DMF (3 mL)

added and the solution is added to the filtered resin. Dimethylaminopyridine (5 mg, 0.04 mmol) is added to the mixture and the reaction is left for 60 minutes. The resin is filtered and washed with DMF (3 x 6 mL), MeOH/DCM (1:1) (3 x 6mL), and finally DCM (3 x 6 mL). The resin is further dried by air.

Solid Phase Step 2: Removal of the Boc group

The resin (1.1 g) is treated with a solution of trifluoroacetic acid (3 mL) in DCM (3mL) for 2 minutes. The resin is then filtered and washed with DCM (5x 6mL).

Solid Phase Step 3

DCM (6mL) is added to the resin (1.1 g) followed by diisopropylethylamine (0.65 mL, 3.7 mmol) and triphosgene (90 mg, 0.25 mmol). After 10 minutes the solvent is filtered and the resin washed with DCM (3 x 6 mL). Aniline (186 mg, 2 mmol) is dissolved in DCM (4 mL) and the solution added to the resin. After 30 minutes the resin is filtered, washed with DCM (4x 4mL) and air dried.

Solid Phase Step 4

The resin (1.1 g) is treated with piperidine/DMF (1:1) (5 mL) for 5 minutes. The resin is filtered and washed with DMF (3 x 6 mL), MeOH/DCM (1:1) (3 x 6mL), and finally DCM (3 x 6mL). DCM (6mL) is added to the resin followed by diisopropylethylamine (0.65 mL, 3.7 mmol) and triphosgene (90 mg, 0.25 mmol). After 10 minutes the solvent is filtered and the resin washed with DCM (3 x 6 mL). 4,6-Benzylidene-2-deoxy-2-*N*-acetamido-1-deoxy-1-amino-alpha-D-muramic acid (155 mg, 0.4 mmol) is dissolved in DMF (4 mL) and the solution added to the resin. After 12 hours the resin is filtered and washed with DMF (3 x 6 mL), MeOH/DCM (1:1) (3 x 6mL), and finally DCM (3 x 6 mL). The resin is further dried by air.

Solid Phase Step 5

A solution of aqueous NaOH (1M, 0.2 mL) and MeOH (2mL) is added to the resin and the reaction left for 40 min. The resin is filtered and washed with MeOH (3 x 6mL). The filtrates are combined, neutralized with 0.1M HCl and solvent evaporated.

The target product was detected by LCMS at m/z 658 (M+H), Molecular Weight calc. For $C_{31}H_{39}N_5O_{11}$: 657 g/mol.

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

References cited herein are listed on the following pages, and are incorporated herein by this reference.

REFERENCES

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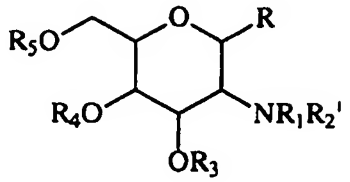
CLAIMS:

1. A monosaccharide compound of general formula I



I

in which the monosaccharide ring is of the glucosamine or galactosamine configuration;

R_4 and R_5 are hydrogen or together form an optionally substituted benzylidene acetal in which the optional substituent is chosen from halo, azido, alkoxy, nitro or alkyl;

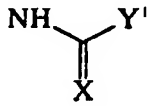
R_3 is hydrogen; optionally substituted glycolate or optionally substituted lactate or derivatives thereof; or a carboxylic acid mimetic;

R_1 is optionally substituted acyl, optionally substituted benzoyl, optionally substituted biphenylcarbonyl, heteroaryl acyl, optionally substituted bicycloacyl, optionally substituted bicycloheteroacyl, sulfonamide, urea or carbamates;

R_2' is hydrogen;

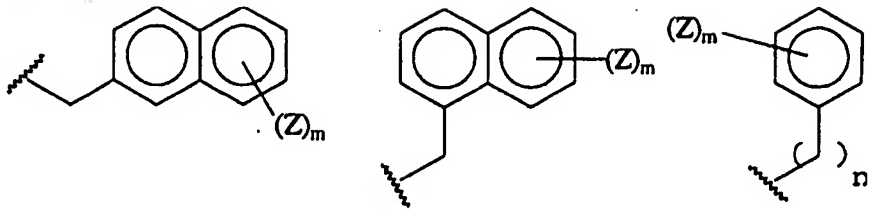
R_1 and R_2' together form succinimide, maleimide or optionally substituted phthalimide;

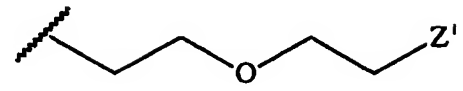
R is N_3, O-Y,

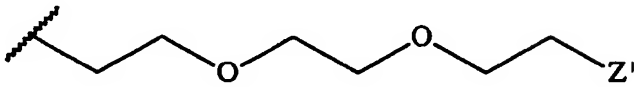


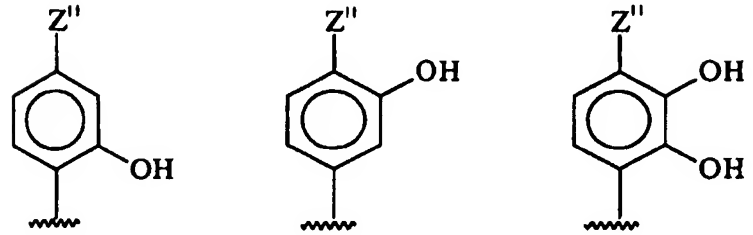
or -NH-SO_2-Y"

in which Y is









in which Z is positioned on one or both of the aromatic rings of the bicyclic structures and is independently selected from OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine and guanidinium;

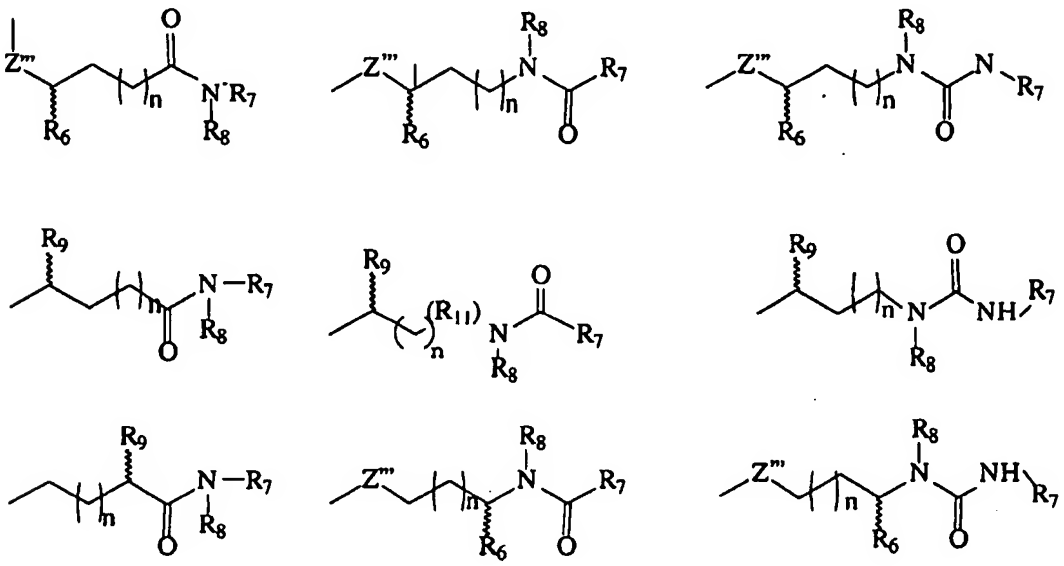
n is 0 or 1

m is an integer of 0 to 3;

Z' is halo, optionally substituted S-aryl, optionally substituted S-heteroaryl, optionally substituted aryl or optionally substituted heteroaryl; Z'' is optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

X is O, NH or S;

Y' is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted arylalkyl, optionally substituted heteroaryl alkyl,



in which Z''' is O,NH or S;

R_6 is H, $CONH_2$ or COOH ;

n is an integer of 0 to 4 ;

R_7 is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl or optionally substituted heteroarylalkyl

R_8 is H, OH, NH_2, alkyl, alkenyl or alkynyl;

R_9 is H, OH, NH_2, or $NHCO-R_{10}$ in which R_{10} is an optionally substituted alkyl;

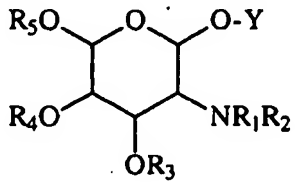
R_{11} is an optionally substituted alkylene, optionally substituted cycloalkyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl; and

Y'' is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkyl, optionally substituted arylalkyl or optionally substituted heteroaryl alkyl,

derivatives thereof, tautomers thereof and/or isomers thereof.

2. A compound according to claim 1 in which the optional substituents are selected from at least one of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine, guandinium and peptidomimetics.

3. A compound according to claim 1 or claim 2 which has the formula Ia



Ia

in which the monosaccharide ring is of the glucosamine or galactosamine configuration and the anomeric centre is either the α or β configuration;

R_5, R_4 and R_3 are as defined in claim 1;

R_2 is hydrogen;

R_1 is

(i) C_{2-8} acyl which is optionally substituted with one or more OH, SH, CF_3, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, aryloxy, SO_2NH_2, amidine or guanidinium;

(ii) a benzoyl group which is optionally substituted with one or more OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium;

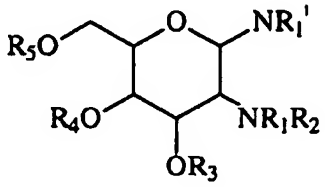
(iii) a biphenylcarbonyl group which is optionally substituted on either one or both of the aromatic rings with one or more of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium; or

(iv) a heteroaryl acyl, sulfonamide, urea or carbamate;

R_1 and R_2 together form optionally substituted succinimide, optionally substituted maleimide or optionally substituted phthalimide;

Y is as defined in claim 1 in which the optional substituents for Z' or Z'' are at least one of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, aryloxy, SO_2NH_2, amidine or guanidinium.

4. A compound according to claim 1 or claim 2 which has the formula Ib



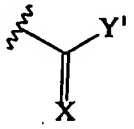
Ib

in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric centre is either of the α or β configuration;

R_5, R_4 and R_3 are as defined in claim 1;

R_2 and R_1 are as defined in claim 3;

R_1' is N_2 or

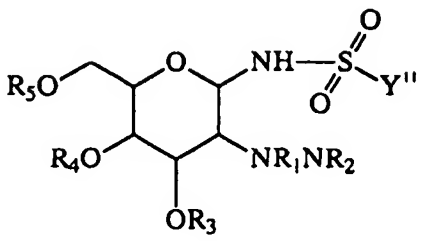


in which

X is O, NH or S; and

Y' is as defined in claim 1 in which R_7 is optionally substituted with at least one of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium.

5. A compound according to claim 1 or claim 2 which has the formula Ic



Ic

in which the monosaccharide ring substitution is of the glucosamine or galactosamine configuration and the anomeric center is either the α or β configuration;

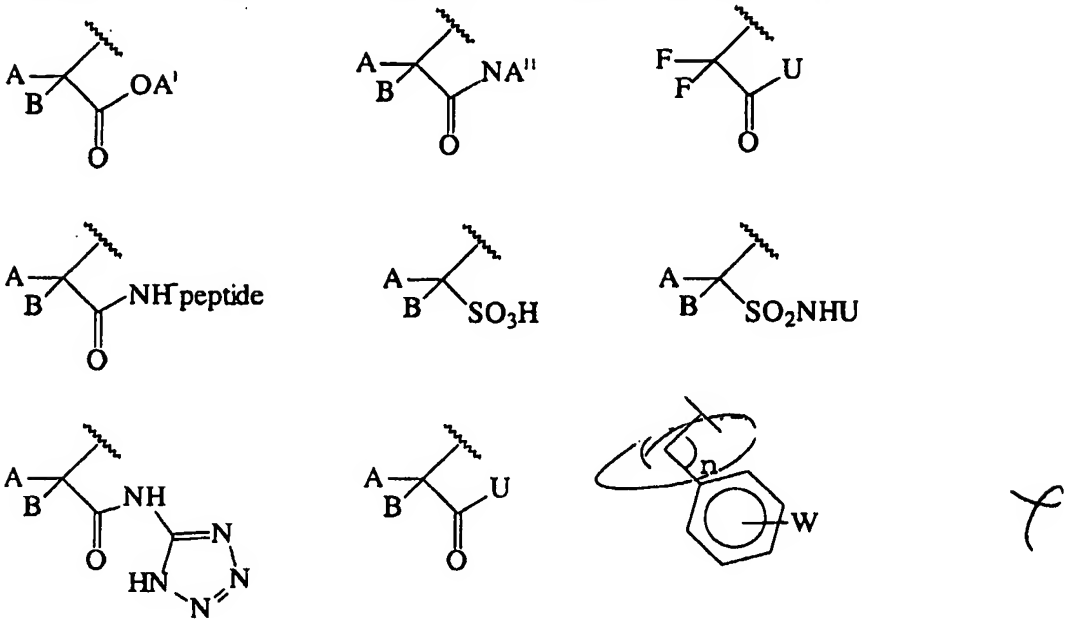
in which R_5, R_4 and R_3 are as defined in claim 1;

R_2 and R_1 are as defined in claim 3;

Y'' is as defined in claim 1 and is optionally substituted with one or more OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium.

6. A compound according to any one of the preceding claims in which the glycolate or lactate or derivatives thereof are substituted with at least one amino acid or peptidomimetic.

7. A compound according to any one of the preceding claims in which the carboxylic acid mimetic is



in which A and B are independently hydrogen, alkyl, trihaloalkyl or halo;

A' is hydrogen or alkyl;

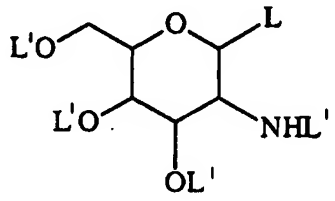
A'' is hydroxy, optionally substituted carboxy or oxyaryl;

U is hydrogen, aryl, heteroaryl, alkyl, alkenyl or alkynyl each of which are optionally substituted with one or more of OH, SH, CF_3, alkyl, alkenyl, alkynyl, NO_2, halo, SO_3H, NH_2, CO_2H, azido, nitroso, alkoxy, SO_2NH_2, amidine or guanidinium; and

W is hydrogen or an acidic or acid mimetic or forms a carbocyclic or heterocyclic ring.

8. A compound according to any one of the preceding claims in which the acidic or acid mimetic is OH, SH, CF_3, NO_2, halo, SO_3H, CO_2H, azido, nitroso, alkoxy or SO_2NH_2.

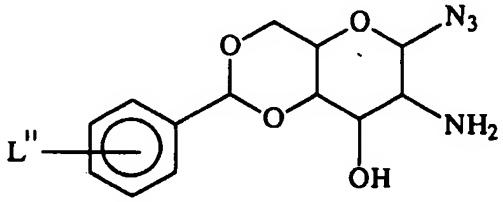
9. A method for the preparation of a compound of general formula I as defined in any one of the preceding claims, comprising the step of glycosylating an intermediate compound of formula IV,



IV

in which L is a leaving group and L' is a protecting groups with an alcohol or phenol acceptor.

10. A method for the preparation of a compound of formulae Ib or Ic, comprising the step of acylating an intermediate compound of general formula V



V

in which L'' is hydrogen, NO_2, halo, azido or alkoxy.

11. A method of screening for antibacterial or antibiotic compounds comprising the steps of:

(a) forming a combinatorial library comprising a compound of the formula I as defined in any one of claims 1 to 8; and

(b) testing the combinatorial library for antibacterial or antibiotic activity.

12. An antibacterial or antibiotic compound identified using the method defined in claim 11.

Figure 1 HPLC chromatogram and mass spectrum

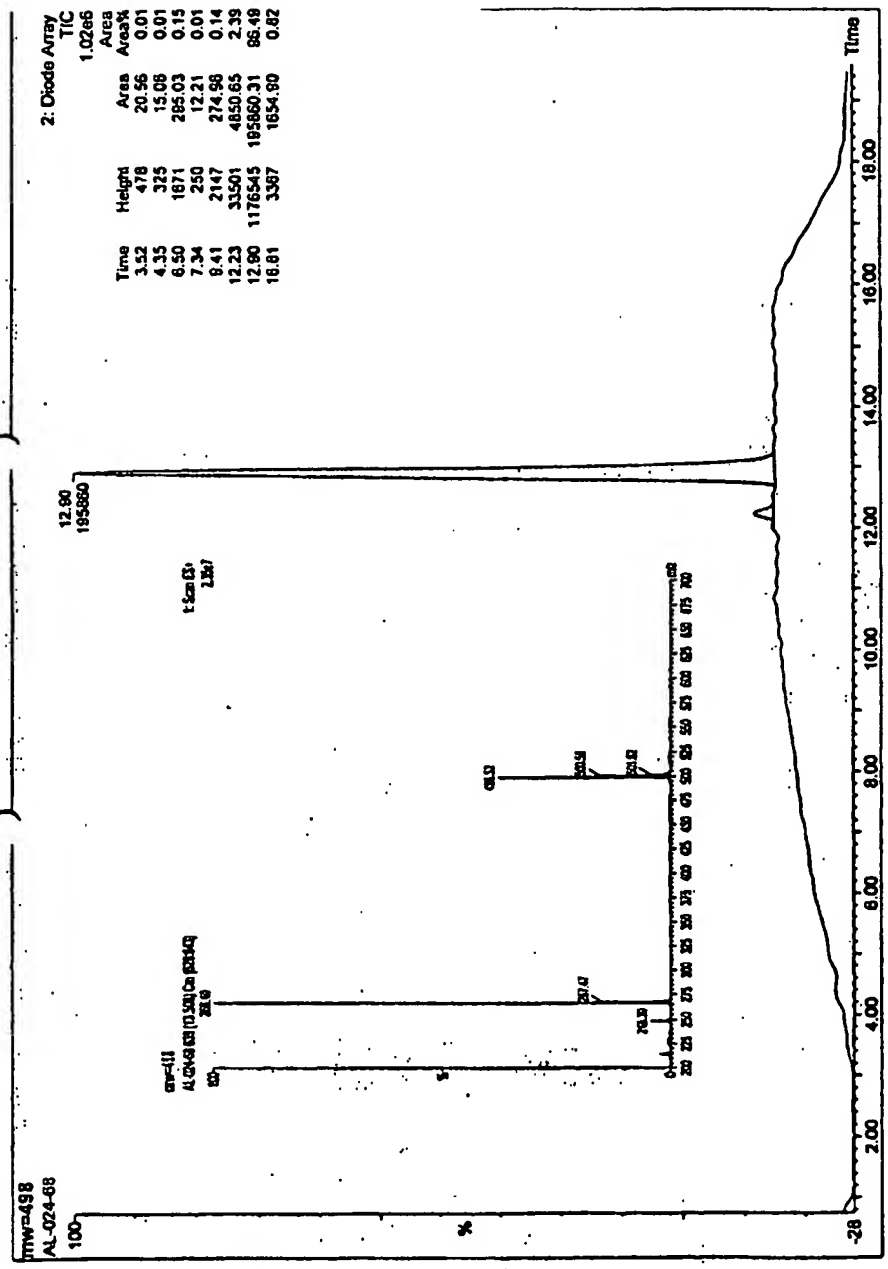


Figure 2 HPLC chromatogram and mass spectrum

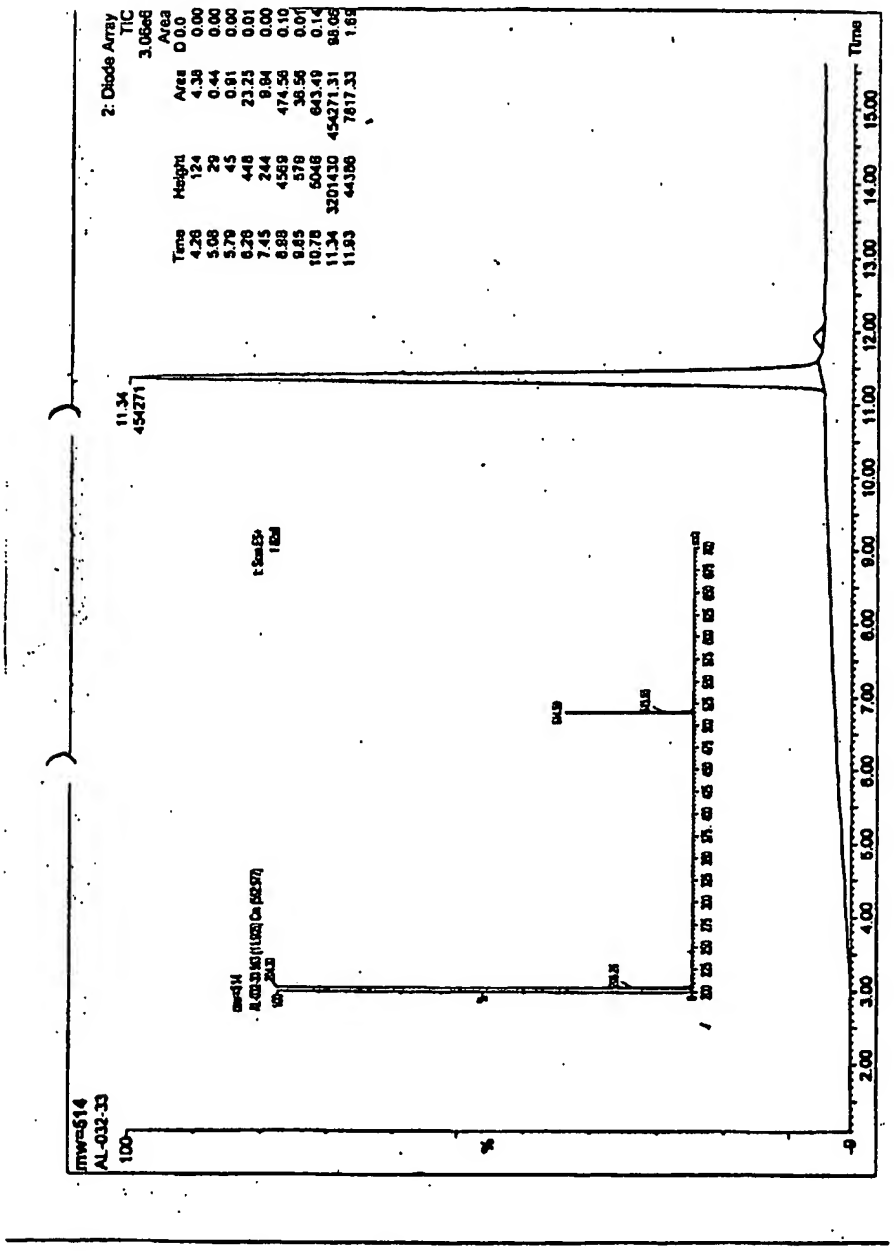
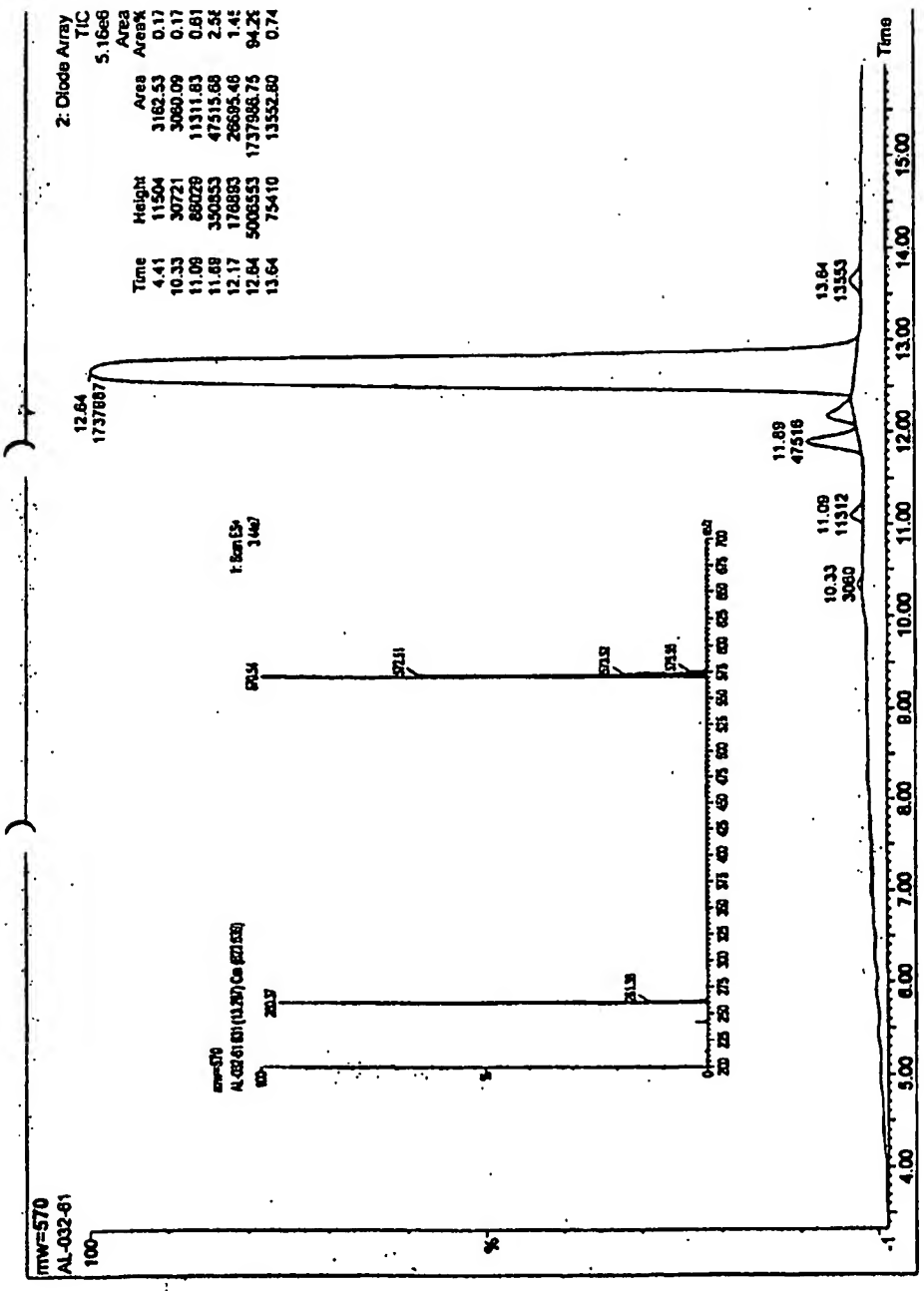


Figure 3 HPLC chromatogram and mass spectrum



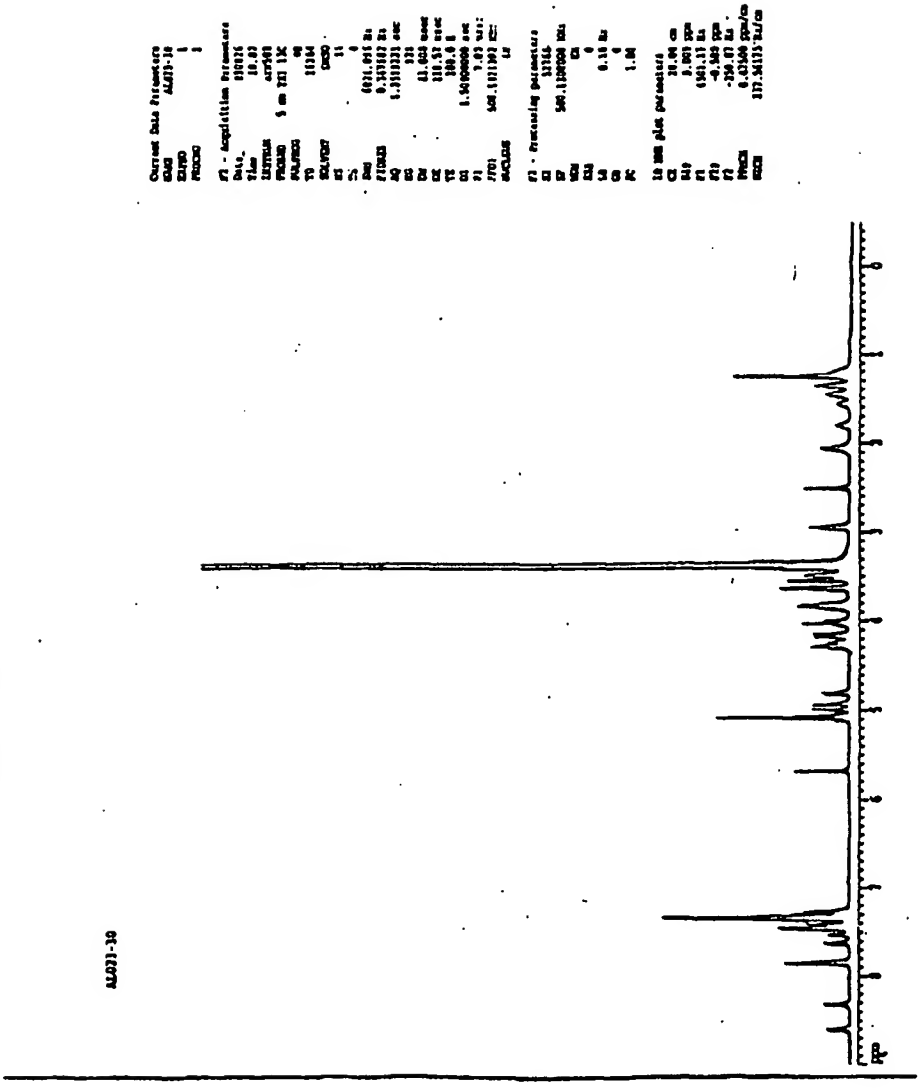


Figure 4a ^{1}H nmr spectrum

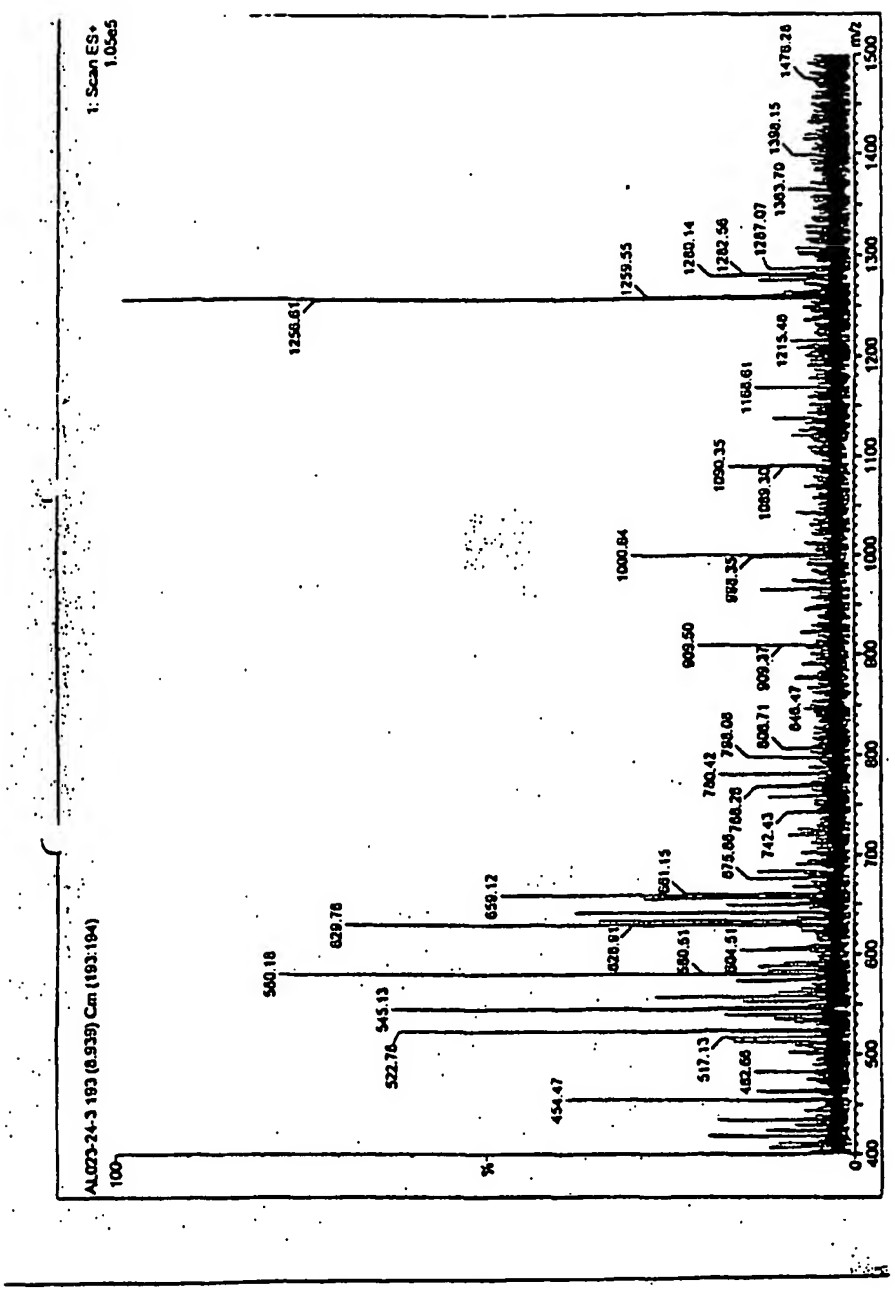


Figure 4b mass spectrum

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01307

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07H 15/18, 15/12, 9/04, 5/06, 15/26, 13/12; A61K 31/7008; A61P 31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN File Registry and CA, Substructure search and key words "antibacter? or muramyl or combinatorial or library".

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstract 133:223029 & G. LIU et al., Bioorg. Med. Chem. Lett. (2000), 10(12), 1361-1363. See abstract and CAS Registry Numbers 292150-07-3, 292150-08-4, 292150-09-5, 292150-10-8, 292150-11-9, 292150-12-0, 292150-13-1, 292150-14-2, 292150-15-3, 292150-16-4, 292150-17-5, 292150-18-6, 292150-19-7, 292159-39-8.	1-12
X	Chemical Abstract 129:216855 & WO 9838197 (ALCHEMIA PTY LTD), 3 September 1998. See abstract and CAS Registry Number 13343-62-9.	1-12
X	Chemical Abstract 123:170109 & V. O. KURYANOV et al., Bioorg. Khim., 1994, 20(4), 439-77. See abstract.	1-12

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 2001	- 7 JAN 2002
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **L.F. MCCAFFERY** Telephone No : (02) 6283 2573

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01307

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstract 134:178795 & S-D ZHANG et al., Pept.: Biol. Chem., Proc. Chin. Pept. Symp., 5th 1998, Pub. Kluwer Academic Publishers, Neth. See abstract and CAS Registry Numbers 15892-26-9, 39524-05-5, 325728-17-4, 325728-18-5, 325728-19-6, 325728-20-9, 325728-21-0, 325728-23-2, 325728-24-3, 325728-25-4, 325728-26-5, 325728-27-6, 325728-28-7, 325728-29-8, 325728-30-1, 325728-31-2, 325728-32-3, 325728-33-4, 325728-34-5, 325728-35-6, 325728-36-7, 325728-37-8, 325728-38-9, 325728-39-0, 325728-40-3, 325728-41-4, 325728-42-5, 325728-43-6, 325728-44-7, 325728-45-8, 325728-46-9, 325728-47-0, 325728-48-1, 325728-49-2, 325728-50-5, 325728-51-6, 325728-52-7, 325728-53-8, 325728-54-9, 325728-55-0, 325728-56-1, 325728-57-2, 325728-58-3, 325728-59-4, 325728-60-7, 325728-61-8, 325728-62-9.	1-12
X	Chemical Abstract 113:212524 & S. J. HECKER et al., J. Org. Chem., 1990, 55(24), 6051-4. See abstract.	1-12
X	Chemical Abstract 78:4456 & J. M. PETIT et al., Carbohyd. Res., 1972, 24(2), 415-425. See abstract.	1-12
X	Chemical Abstract 121:109485 & T. WIEMANN et al., Carbohyd. Res., 1994, 257(1) C1-C6. See abstract and CAS Registry Numbers 156875-97-7 and 156875-98-8.	1-12
X	EP 15468 B1 (TAKEDA CHEMICAL INDUSTRIES LTD), 17 September 1980. See Examples 1(ii), 16(iii), 16(iv), and 23, and Table 2, compounds 5, 6, 8, 15, 16, 23, 24, 33, 34 and 40.	1-12
X	EP 14159 B1 (MERCK & CO), 6 August 1980. See Examples and Claims.	1-12
X	EP 97506 A2 (M. J. AHERN), 4 January 1984. See Claim 1.	1-12
X	US 4866035 A (P. L. DURETTE), 12 September 1989. See Examples and Claims.	1-12
P,X	WO 01/51499 A (ALCHEMIA PTY LTD), 19 July 2001. See compounds 30 and 31.	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01307

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **1-12 (all in part)**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

An economical search could not be carried out for the present compounds. Moreover, a fairly conservative substructure search of these compounds resulted in too large a number of Chemical Abstracts to be economically displayed. The present search report cites only a small selection of the answers that anticipate the present claims.

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01307

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
EP	15468	AT	2149	CA	1185237	DE	3061468
		JP	55115895	US	4314998		
EP	14159	AT	1341	CA	1185236	DE	3060658
		DK	334/80	IE	49147	JP	55102599
		US	4256735	US	4377570		
EP	97506	AU	14988/83	DK	2838/83		
US	4866035		NONE				
WO	200151499	AU	200126542				

END OF ANNEX